SCIENCE

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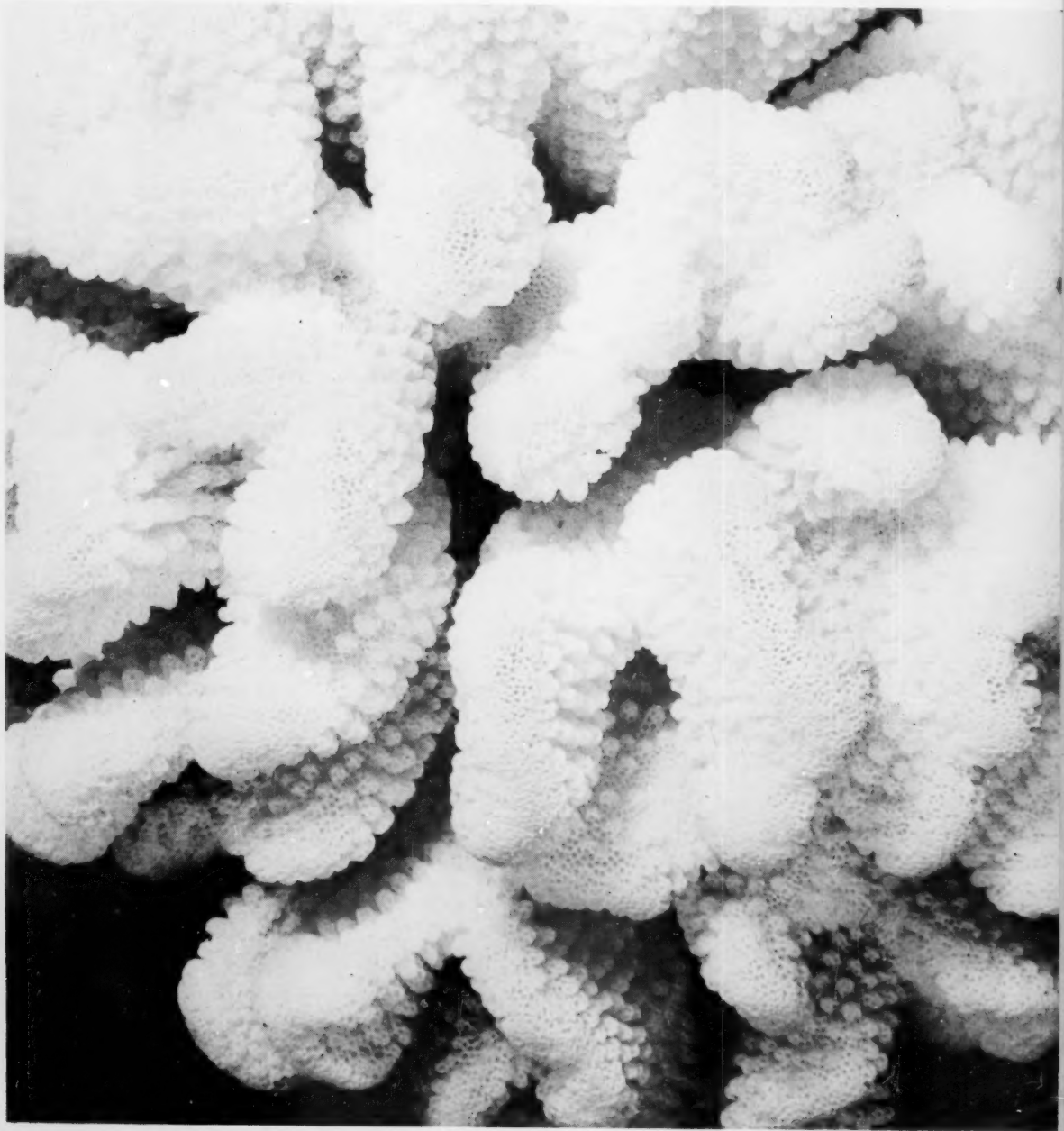

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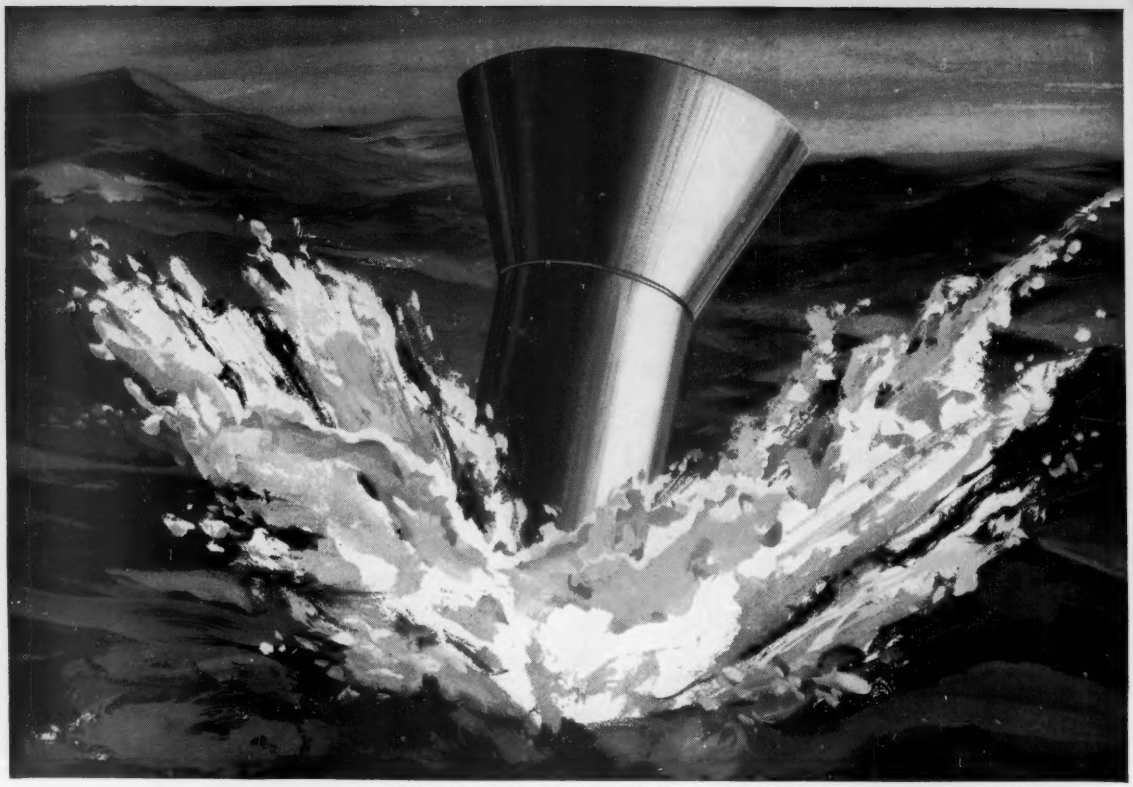

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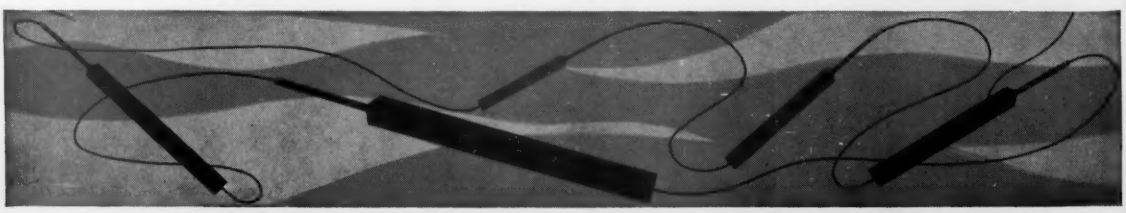

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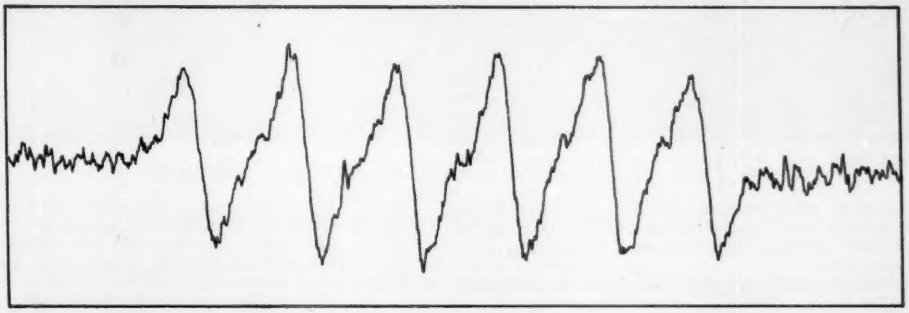

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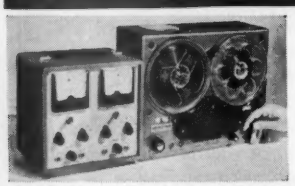

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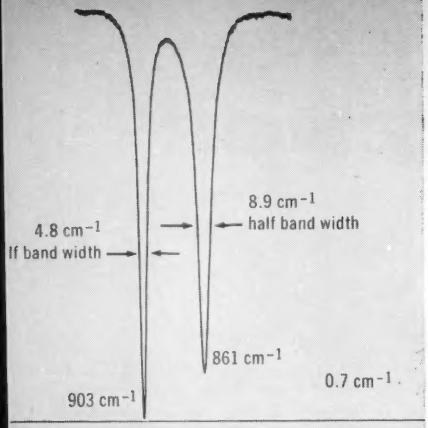
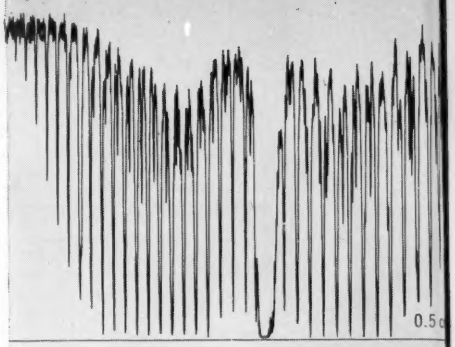
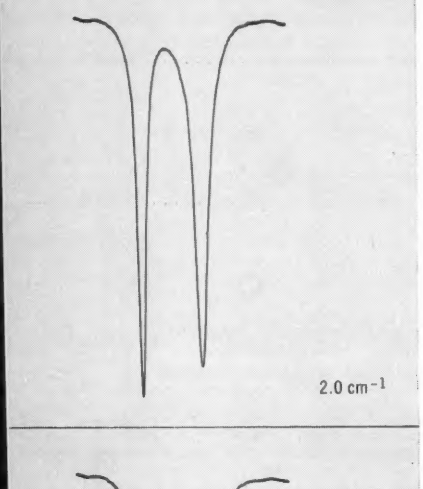
Cover Skeleton of stony coral from the Great Barrier Reef, Australia. [W. A. Hilton, Department of Zoology, Pomona College, Claremont, Calif.]

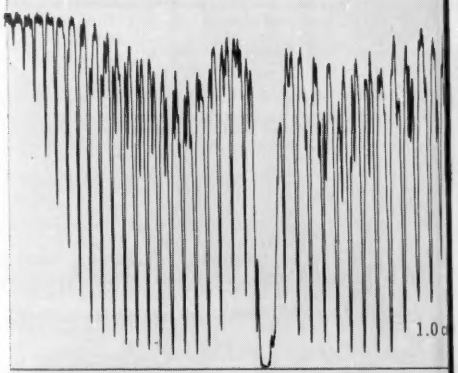


Left, spectrum of a 0.21 mm. thickness sample of spectro-grade cyclohexane demonstrates the importance of high resolution for routine *quantitative analysis.*

Right, the C-H stretching band of methane illustrates the increased research *data obtainable with high resolution spectroscopy.*







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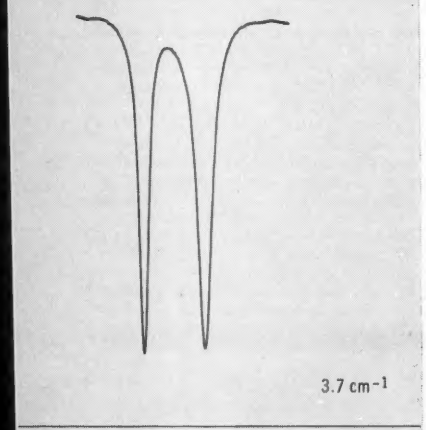

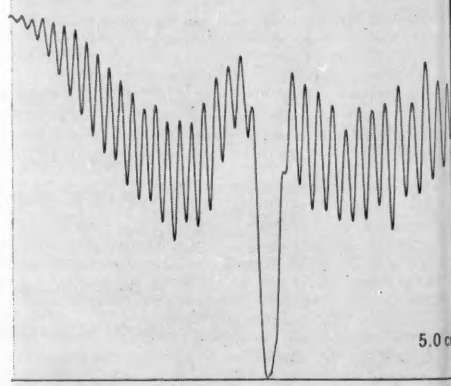

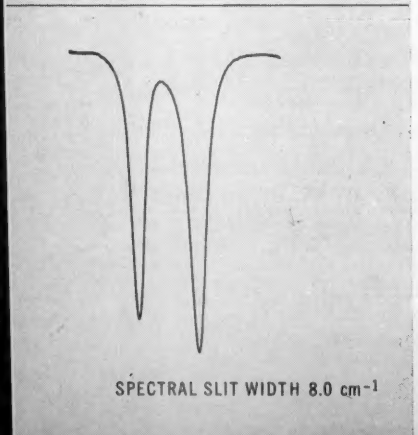

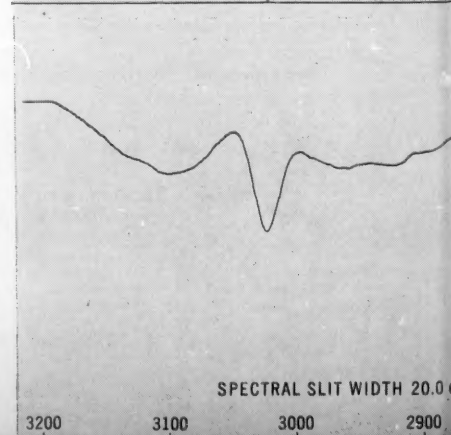

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One in Eighteen Thousand

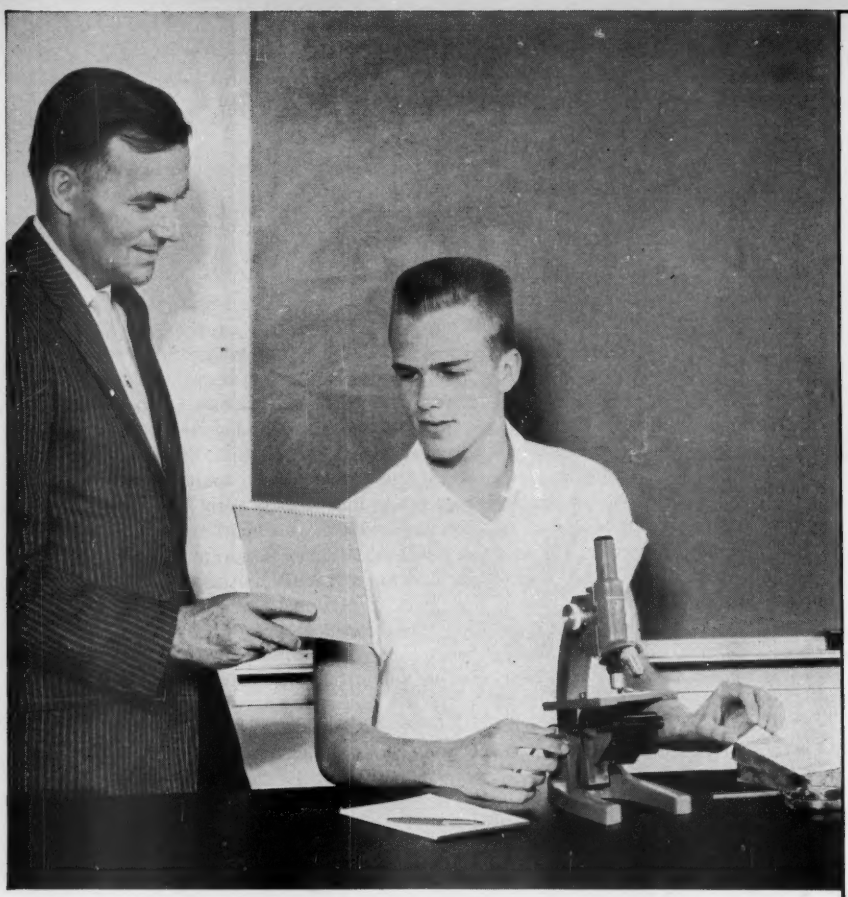
For many scientific purposes an event that happens only once in ten or twenty thousand tries is statistically insignificant; a probability of .0001 or .00005 may, in many cases, be safely disregarded. But in other cases, the focus of interest may be on the unusual event itself—say, a mutation of a gene or the appearance of a strange nuclear particle. The event, though very infrequent, may be of significant interest.

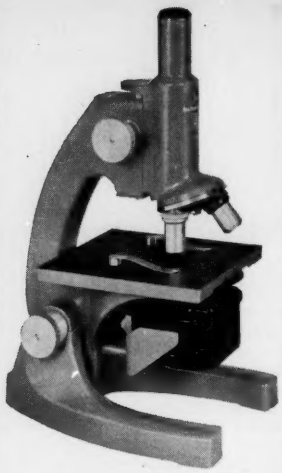
A roughly analogous situation occurs in the administration of human affairs, but the difference lies in the way the event is considered. If the event is unwanted, then steps may be taken to try to prevent its recurrence. The case of Edward L. Yellin is a rare event of this kind. Mr. Yellin, a graduate student in mechanical engineering at the University of Illinois, was given a National Science Fellowship for the academic year 1961–62. His academic record, although it was interrupted by 8 years of work in a steel mill, was excellent; his recommendations were high; and his application included a properly signed and sworn disclaimer of subversive affiliations. Last March, at the time the award was made, there was no reason for the National Science Foundation to suppose that the fellowship was undeserved.

Early in April the House Un-American Activities Committee informed the Foundation that in 1958 Mr. Yellin, who had allegedly been a member of the Communist Party, refused to answer any questions about his activities on the basis of the First Amendment. The Committee also charged that Mr. Yellin, in applying for work at the steel mill, had not indicated that he had had 2 years of college education. Mr. Yellin was cited for contempt of Congress and convicted in 1960. The conviction was upheld upon appeal to a Circuit Court and is now being appealed to the Supreme Court. As a consequence, Mr. Yellin was suspended for 10 days by the University of Illinois. After an unpublicized hearing, at which he is said to have answered all questions fully and frankly, he was reinstated. The clear implication of this action is that the examining committee at Illinois was convinced that Mr. Yellin was morally and intellectually qualified to continue as a student. But the Foundation was not informed of any of these actions or conclusions.

After hearings last week at which members of the Un-American Activities and the House Science and Astronautics committees questioned Foundation officials about the case, the Executive Committee of the National Science Board was convened and the fellowship was revoked on the ground that there was a possibility that the term would be interrupted. Opinion about the wisdom of this action is divided. According to one view, the fellowship might have been suspended to give time for a careful consideration of policy to govern this and future cases. The policy question is: Is conviction for a criminal offense adequate grounds for denying or revoking a fellowship? The law governing fellowships says that they shall be awarded "solely on the basis of ability." The Foundation interprets ability to include, in addition to intellectual capacity, motivation, independence, objective judgment, accuracy, and integrity. Mr. Yellin's record throws doubt upon his qualifications under this broad definition of ability.

The remedy suggested by this first case of its kind in the 18,000 fellowships that the Foundation has awarded is a simple one. To minimize the chance that so rare an event will occur again the Foundation need only include on its application form a question about the criminal record of the candidate. Cases could then be decided on their merits: some crimes are more relevant than others.—G.DuS.





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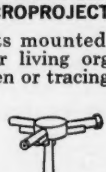

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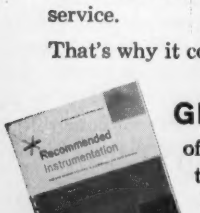

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CURRENT PROBLEMS IN RESEARCH

Protein Malnutrition in Young Children

Malnutrition is still a major factor in the high morbidity and mortality in underdeveloped areas.

Nevin S. Scrimshaw and Moisés Béhar

It is disconcerting to discover that even today in many parts of the world half of the children born in low-income groups die before they are five years of age and that a significant proportion of these deaths are attributable directly or indirectly to malnutrition. It is now evident that most deaths from protein malnutrition occur after weaning, and that the mortality of children from one to four years old in a country is the best index of the seriousness of protein malnutrition (*1*). For example, the mortality of children one to four years of age in the United States and in most countries of Western Europe is now around 1 per 1000, while in most technically underdeveloped countries the proportion varies from 10 to 45 per 1000.

Careful investigation was made of a series of individual deaths of children in four rural Guatemalan towns in which the mortality of the 1- to 4-year age group was 50.3 per 1000. It was found that nearly two-fifths died from the deficiency disease kwashiorkor, and that the remaining deaths were nearly equally attributable to infectious diarrhea and to systemic infections very few of which would have been fatal if the children had been well nourished (*2*).

The widespread occurrence of kwashiorkor is shown in Fig. 1, but its seriousness is better indicated by the data in Table 1, which shows the mortality of children from one to four years of age in representative countries where kwashiorkor is rare or unknown as contrasted with deaths occurring in countries where kwashiorkor is common.

Another form of severe malnutrition in children, which is often fatal, is marasmus. This disease develops when the child is deprived not only of adequate protein but also of calories and other nutrients. For both physiological and cultural reasons, marasmus is more common in children below one year of age, while kwashiorkor is more prevalent in children during the second and third years.

Research on the problem of protein malnutrition in children is now being actively carried on throughout the world, and this article attempts to define the present status of our knowledge in a still dynamic and rapidly progressing field (*3*).

Clinical Characteristics

Protein deficiency in growing children cannot be described as a single clinical syndrome because it is usually associated with some degree of calorie inadequacy. The relative magnitude of this deficiency and of deficiencies of other nutrients determines the resulting clinical picture (*4*). The clinical spectrum of severe protein deficiency ranges from deficiency accompanied by an adequate or even excessive caloric intake to that accompanied by a lack of calories so great that this lack becomes the limiting factor and few signs and symptoms of protein deficiency are apparent. The principal reason why investigators cannot fully agree on the line of demarcation between kwashiorkor and marasmus is the difficulty of establishing limits within this continuous spectrum, which is illustrated diagrammatically in Fig. 2. Cases combining characteristics of both are frequently identified as "marasmic kwashiorkor" (*5*).

The clinical picture depends greatly on the relative degree or intensity of protein and calorie deficiencies. If consideration is limited to the advanced states of each, the main clinical signs and symptoms of the kwashiorkor type are pitting edema (which is a *sine qua non* of the diagnosis), a variable degree of dermatosis characterized by hyperkeratosis, hyperpigmentation, and desquamation, which are illustrated in Fig. 3.

The hair shows three types of alteration: its implantation is affected, so that it falls out spontaneously or can be painlessly removed with little effort. It becomes dry, thin, and brittle, and curly hair tends to straighten. The color is also usually altered. When periods of malnutrition alternate with periods of relatively adequate dietary intake, depigmented bands appear in the hair. The name "flag sign" has been applied to this phenomenon, which is illustrated in Fig. 4. Changes paralleling those in the hair may also be observed in the nails.

Psychic changes always occur to some extent, with a mixture of apathy and irritability prevailing. Anorexia and diarrhea are also very common. Even when clinical diarrhea is not present, the stool volume is greater than in normal children, a finding characteristic of malabsorption syndrome. Muscular hypotonicity is also frequently observed.

Dr. Scrimshaw is the director of the Institute of Nutrition of Central America and Panama (INCAP), Guatemala. Dr. Béhar is assistant director.

Fig. 1. Geographical distribution of kwashiorkor.

In marasmus the predominant signs are retardation in growth and development, as evidenced by height and weight and bone maturation; extreme muscular wasting; and a virtual lack of subcutaneous fat. It should be noted, however, that even in children at the kwashiorkor extreme of the spectrum, such as those described in Jamaica as "sugar babies" (*5*), there is some growth retardation and muscular wasting. The contrasting appearance of children with kwashiorkor and marasmus is shown in Figs. 5 and 6.

Signs and symptoms attributable to specific vitamin or mineral deficiencies are commonly observed both in children with kwashiorkor and in those with marasmus. Examples are eye changes characteristic of vitamin A deficiency and lesions of the conjunctiva and oral mucosa associated with riboflavin deficiency. The frequency of such symptoms varies greatly from one region to another. They appear to be superimposed on the basic manifestations of protein and calorie deficiency and are not, therefore, considered to be characteristics of these syndromes.

Hematology. Some degree of anemia is always found in kwashiorkor, although it is usually mild, unless another major cause of anemia is also present. All the major types of anemia may occur in children with kwashiorkor (*6*). The type depends primarily on whether a deficiency of iron, vitamin B_{12} or folic acid or an infection is superimposed on the protein deficiency. The exact role of protein deficiency per se in the production of some types of anemia is still not known.

Other alterations in the blood include a tendency to leucopenia or diminished leucocytic response to infections, as well as some inconstant alterations in the coagulation system (*7*).

Biochemistry and Physiology

Protein. Low total serum protein is a diagnostic characteristic of kwashiorkor. It is due almost entirely to a low level of albumin and is sometimes partially obscured by a relatively high level of gamma globulin resulting from a concurrent infectious process. There is a tendency for the beta-globulin fraction to be both relatively and absolutely decreased; a relative increase in the alpha-2 globulin has also been found (*8*). Studies with I^{127}-labeled albumin indicate that the lowering of this fraction is due to a decrease in rate of synthesis and not to abnormal catabolism (*9*).

Total α-amino nitrogen in plasma is abnormally low because most amino acids are present in decreased amount. The greatest reductions are found in tryptophan, cystine, valine, tyrosine, and methionine. Low levels of urea in both blood and urine indicate decreased protein metabolism. There is also evidence that the synthesis of antibodies is inhibited in kwashiorkor (*10*).

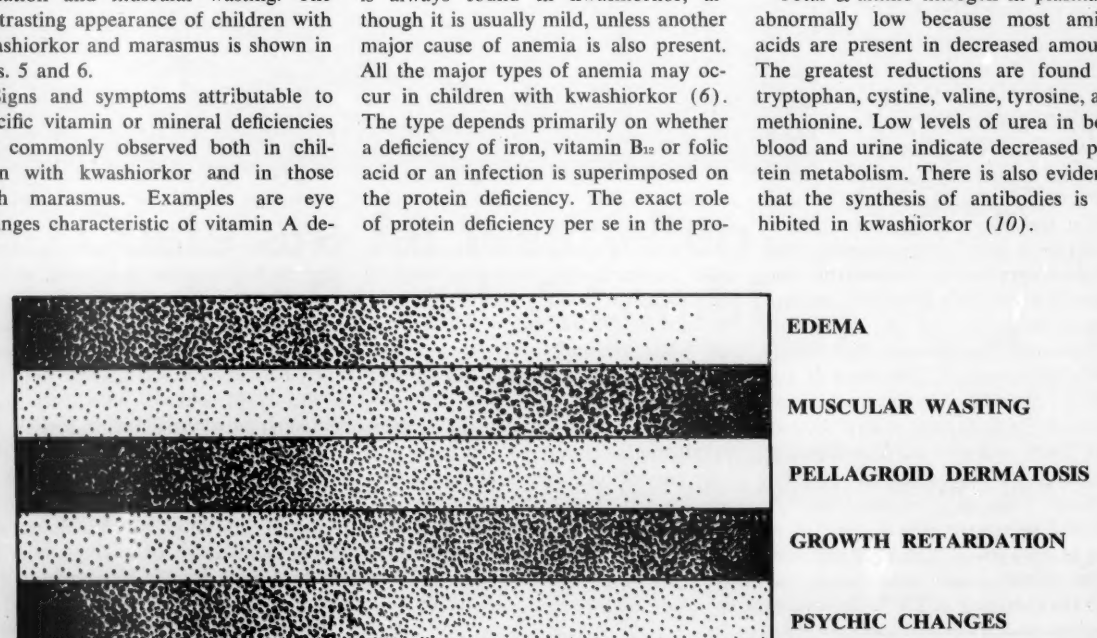

Fig. 2. Schematic representation of the interrelationship of kwashiorkor (*K*) and marasmus (*M*).

Fig. 3. Edema and skin lesions in a child with kwashiorkor.

In acute cases of kwashiorkor, the level of blood creatinine tends to be relatively high, presumably because of reduction in urinary excretion, which is even too low to be accounted for by the decrease in muscle mass.

A very marked increase in the proportion of urinary nitrogen excreted as purine derivatives has been taken as evidence of cellular breakdown in kwashiorkor (*11*). Other abnormal substances in the urine, which indicate impairment of important metabolic pathways, are β-aminoisobutyric acid and ethanolamine (*12*).

The only tissue proteins measured have been those of liver and muscle. It appears that, although the liver protein in kwashiorkor is greatly diluted by fat, it is not decreased in absolute amount in relation to body size. However, a lowered ratio of nitrogen to deoxyribonucleic acid has been reported (*13*), suggesting a true loss of protoplasmic nitrogen. In any case, the level of nitrogen in the liver of children with kwashiorkor is markedly decreased over that for normal children of the same age. There is also a marked loss of muscle nitrogen in kwashiorkor, the degree depending largely upon the degree of preexisting marasmus.

Lipids. All the various lipid fractions which have been determined in blood of children with kwashiorkor, including neutral fat, fatty acids, phospholipids, and cholesterol, have been found to be low, and levels of these substances rise rapidly in the course of treatment. An increase in fat content of the liver, found by gross and microscopic examination, is another diagnostic criterion. In true marasmus, on the other hand, the amount of liver fat is decreased.

Carbohydrate. Blood glucose levels are generally low. Although glucose tolerance is sometimes reduced, so that the diabetic type of glucose tolerance curve is observed, this is not a constant feature of the disease (*14*).

Enzymes. The protein deficiency of kwashiorkor is severe enough to cause profound alterations in the activities of many enzymes (*15*). In marasmus, enzyme activity is apparently not affected.

In the acute stage of kwashiorkor, lipase, trypsin, and amylase activities in the duodenal secretion are lowered almost to zero, and marked reductions in serum pseudocholinesterase, amylase, carbonic anhydrase, and alkaline phosphatase are recognized characteristics of the syndrome. The activity of these enzymes returns rapidly to normal with the administration of an adequate diet. Alkaline phosphatase levels, however, show a slight further drop before rising with therapy.

The activity of a number of enzymes has also been measured in fresh liver tissue obtained by needle biopsy from children with kwashiorkor (*16*). The outstanding finding is a decrease in xanthine oxidase activity per unit of protein, although cholinesterase and D-amino acid oxidase activity are also definitely lowered. In one case, in which death occurred soon after hospitalization, diphosphopyridine nucleotide cytochrome *c* reductase activity was also decreased. In the remaining cases, the activity of this enzyme and of glycolic acid oxidase, both riboflavin-dependent, was not affected, nor were the pyridine nucleotide-dependent enzymes lactic dehydrogenase and malic dehydrogenase or the pyridoxine-dependent transaminase. Alkaline phosphatase activity in the liver is generally increased. These findings suggest that, although the activity of many key enzymes is maintained even in the presence of extreme protein deficiency, some are sufficiently affected to initiate the train of events culminating in death.

Electrolytes and other minerals. Potassium depletion is a major biochemical characteristic of kwashiorkor and is a direct consequence of the protein deficiency (*17*). Other electrolyte changes are secondary consequences of diarrhea (a symptom almost always present in kwashiorkor) or vomiting, which may also accompany the deficiency. Interpretation and correction of electrolyte changes in kwashiorkor is complicated by the abnormal distribution of water and the severe degree of potassium depletion.

Fig. 4. "Flag sign" in the hair of a child recovering from kwashiorkor. The band of depigmentation corresponds to the period of acute deficiency.

There is no evidence of an initially altered calcium-phosphorus ratio in kwashiorkor, nor is there a significant degree of bone hypocalcification. When insufficient calcium is included in the therapeutic diet, tetany due to hypocalcemia may occur during recovery. Magnesium deficiency has recently been reported in kwashiorkor and may also be responsible for some cases of tetany (*18*). It has been postulated that the reduction in intracellular ions may lead to a breakdown of cellular metabolism by interfering with vital enzymatic activities (*19*).

Table 1. Specific mortality rates, per 1000 population, of children 1 to 4 years of age in selected countries (1955–56) (*39*).

Countries where kwashiorkor is rare or unknown	Mortality rate	Countries where kwashiorkor is common	Mortality rate
Argentina	3.8	Colombia	20.3
Australia	1.3	Ecuador	28.8
Belgium	1.6	Egypt	60.7
Canada	1.5	El Salvador	22.7
France	1.6	Guatemala	42.7
Japan	3.8	Guinea	55.4
Netherlands	1.2	Mexico	24.0
Sweden	1.0	Thailand	14.5
United States	1.1	Venezuela	12.5

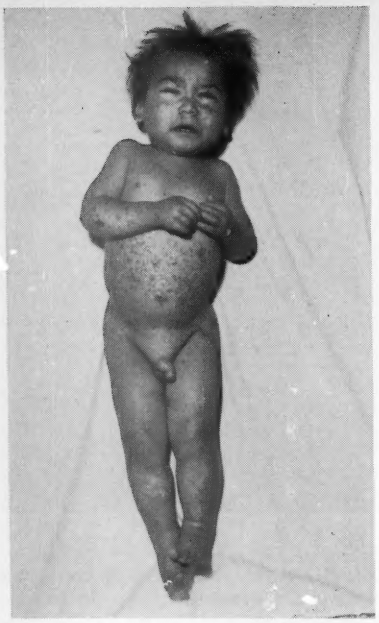

Fig. 5 (left). Child 1 year and 11 months old with kwashiorkor, as observed in Central America. Note the edema, the psychic changes, the changes in skin and hair. Fig. 6 (right). Child 4 years and 5 months old with typical marasmus, showing marked muscular wasting and lack of subcutaneous fat.

Levels of iron and copper are extremely low in the plasma of children with kwashiorkor. The explanation appears to lie in a reduction in transport protein—a hypothesis substantiated in the case of iron by the finding of a low iron-binding capacity (*20*). The iron content of the liver may be increased or decreased, according to the previous dietary history of the child.

Fat-soluble vitamins. Levels of vitamin A and carotene in the serum of children with kwashiorkor are extremely low. It was assumed that this was due to low intake of vitamin A, until recent studies demonstrated that children with acute kwashiorkor upon admission to the hospital did not have an increase in serum vitamin A after a 75-milligram oral dose of vitamin A palmitate. After three to five days of intensive protein therapy, however, a similar dose gave the same sharp increase in serum vitamin A that is found in normal children (*21*). It was also found that, in most cases, serum vitamin A levels rose with protein therapy, even when the diet contained no carotene or vitamin A. Analysis of liver biopsy material demonstrated that this phenomenon occurred whenever there were adequate stores of vitamin A in the liver, and that in those few cases where there was gross depletion of vitamin A in the liver, administration of protein alone produced no serum response (*22*). From this and similar studies, it appears probable that the transport of vitamin A and possibly of vitamin E, which also occurs in abnormally low amounts in blood plasma of children with kwashiorkor, is inadequate because of the lack of a protein carrier.

No vitamin D deficiency has been observed. Little is known about vitamin K levels in kwashiorkor, except that in the majority of cases prothrombin time is not seriously affected.

Water-soluble vitamins. Blood levels of thiamine and riboflavin are within normal limits in children with kwashiorkor. Even though the pigmented skin lesions superficially resemble those of pellagra, there is no evidence of niacin involvement. The urinary excretion of N-methylnicotinamide, in cases in Central America at least, is within normal limits. Levels of serum ascorbic acid are relatively low but are not in the range commonly associated with clinical deficiency (*8*). No significant alterations of levels of vitamin B_{12} in the blood have been found (*23*).

Endocrine function. Children with kwashiorkor have a low urinary excretion of 17-ketosteroids and 17-hydroxysteroids. The latter finding, together with near-normal eosinophil counts, suggests that there is a marked decrease in glucocorticoid activity. In marasmus, on the other hand, the excretion of 17-hydroxysteroids in the urine is normal or high, and eosinophil counts are greatly reduced, suggesting hyperactivity of the adrenal cortex. Further evidence has been obtained from experiments carried out in animals fed diets simulating those of children developing either kwashiorkor or marasmus (*24*).

Cardiovascular function. In the marasmic type of kwashiorkor seen in Central America, a relatively small heart, which rapidly increases in size with treatment, is found upon radiological examination (*25*). Electrocardiographic findings have been reported to show principally low voltage and minor abnormalities, including alterations in the T wave and changes in rhythm (*26*).

Gastrointestinal function. To judge by the volume of feces excreted by children with kwashiorkor, these children suffer from a malabsorption syndrome which is not completely corrected even after some weeks of treatment. Good digestion and absorption of proteins still take place during the acute state, but fat is poorly handled at first. Although fat absorption improves very rapidly as the child recovers, some degree of steatorrhea persists even into late recovery (*27*).

Hepatic function. Despite the marked histological alterations in the liver, the common tests for liver function have been found to give results within normal limits, with the possible exception of Bromsulphalein retention, which is frequently high (*28*).

Renal function. A reduction in renal plasma flow has been reported; this is found particularly when there is dehydration and therefore appears to be related to the diminished volume of circulation. The glomerular filtration rate, as indicated by clearance of inulin and endogenous creatinine, is also reduced (*29*). Although there is some evidence of reduced antidiuretic activity, the mechanism of water retention in kwashiorkor is not yet clear and may be primarily a physiological response of the kidney to the electrolyte and water disturbances.

Neurological function. Electroencephalographic studies have shown diminished voltage and excessively slow rhythmic activity. Some authors have

also reported abnormal focal activity and other alterations (*30*). These abnormalties tend to disappear as recovery progresses.

Gesell tests, or similar procedures for evaluating psychic development, when carried out after a few days of treatment, show marked retardation. It has been reported that when the child has recovered, he reaches normal levels for his age (*31*). Others have reported, however, that the child is still mentally retarded after complete clinical recovery (*32*). The duration of illness and opportunities for learning must be taken into consideration in the interpretation of these data.

Pathology

In kwashiorkor, the liver and the pancreas are the most seriously and constantly affected organs (*8*). The most evident alteration in the liver is a diffused fatty change which starts at the center of the lobule and eventually affects nearly all of the parenchymal cells, as illustrated in Fig. 7. As a result, the sinusoids are generally collapsed. Small acute inflammatory foci may also be present. Although an increase in the reticular fibers is common, we do not believe that true fibrosis has been demonstrated in uncomplicated cases of kwashiorkor.

Atrophic changes in the exocrine pancreas include shrinkage of the acinar cells, reduction in the number of enzyme granules, and a loss of the basal proenzyme plate. In a few severe cases there is a definite increase in fibrotic tissue. The salivary and intestinal glands are similarly affected. The intestinal wall is sometimes so atrophic as to be nearly transparent.

No significant cellular changes in the pituitary have been observed. The thyroid gland contains follicles which are smaller than normal and have cuboidal epithelium. The testes and ovaries show only minimal signs of maturation as compared to those of normal children of the same age. The adrenals tend to be small in size and weight. Histopathologically, two different and opposite patterns are observed in the cortex, one compatible with hypofunction and the other with hyperfunction of these glands.

The skin shows atrophy of the epidermis with a varying degree of hyperkeratosis and parakeratosis. The skin appendages are also atrophic.

The striated muscle shows atrophy, with a varying degree of loss of striation. Usually no anatomical lesions are found in the kidney except, in some cases, a fatty degeneration of the tubules. When there is severe hypokalemia, a typical vacuolar degeneration occurs.

Epidemiology

The major factors involved in the etiology of protein malnutrition are summarized graphically in Fig. 8. They are diverse in nature and include agricultural, economic, cultural, and medical causes.

Food production is, of course, fundamental. In the underdeveloped areas of the world where protein malnutrition is prevalent, production of protein-rich foods, and particularly those of animal origin, is nearly always insufficient to meet the nutritional needs of the population. The per capita availability of these foods in different areas of the world, listed in Table 2, indicates that low-production areas correspond very closely to areas where kwashiorkor is common.

This low production is mainly the result of failure to employ modern techniques of agriculture and animal husbandry. The productive capacity is further reduced by debilitating infectious and nutritional diseases.

The per capita availability of foods does not in itself give an accurate idea of their distribution among the different socioeconomic groups. In addition, the lack of facilities for transportation and preservation often results in a decrease in the availability of animal foods in some areas and among some population groups within a country.

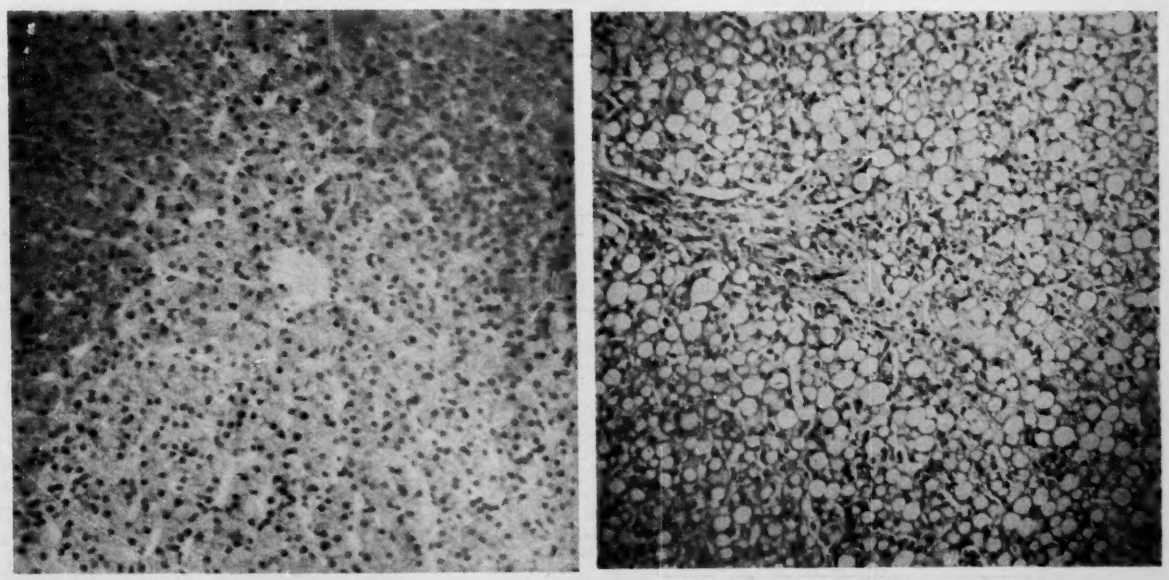

Fig. 7. Normal liver (left) and liver of a child with kwashiorkor (right), in which fat fills each hepatic cell, giving the liver a honeycomb appearance (hematoxylin and eosin stain; × 100).

Table 2. Per capita availability of foods, in grams per day (*40*).

	Countries included (*N*)	Milk	Animal protein	Total protein
Regions where kwashiorkor is unknown or rare				
North America	2	722	64	94
Oceania	2	642	66	98
Western Europe	15	573	43	85
Regions where kwashiorkor is common				
Latin America	7	222	22	62
Near East	3	93	20	84
Africa	5	93	19	65
Far East	6	30	12	51

The availability of food to the family, furthermore, does not accurately indicate its consumption by the individual members. Particularly in populations which do not have enough protein-rich food, small children suffer most from an inequitable distribution within the family. There are many reasons for this, but most of them are due to the mother's ignorance of the nutritional needs of small children and the ways of satisfying them, and from unfortunate cultural beliefs and taboos.

In the areas where protein deficiency is prevalent, most infants are breast-fed for a relatively long time, but without proper supplementation. For several years after weaning, children receive a diet which is often much poorer in proteins than that of any other member of the family. When these children become ill, the protein of their diet is likely to be reduced still more.

A further reduction in diet is often made by the child himself, by failure to eat all the foods actually offered him, because of anorexia, which is presumably the consequence of an infectious process or of the poor diet itself. Anorexia may also develop for psychological reasons when the child receives less attention from the mother than he is accustomed to after the birth of a younger sibling.

The amount of protein absorbed by the child is decreased by heavy intestinal parasitic infections, severe diarrheas, the physical state of the food, the quality of the protein, and the presence of interfering substances. His nitrogen retention is also diminished by such factors as catabolic losses due to infectious processes, the biological value of the protein, and use of protein to meet caloric needs. The amount of nitrogen finally retained by the child determines his nutritional status with respect to protein.

In the classical epidemiological terms of agent, environmental factors, and host factors in the etiology of disease, the agent of kwashiorkor is generally considered to be a deficiency in protein or, more specifically, in the amounts and proportions of the essential amino acids. Of equal importance, however, in determining whether or not the disease appears with a given diet are the environmental factors (such as those determining the availability of protein-rich foods), the stress of infections, and sociocultural factors. Host factors include the decrease in protein requirement per unit of body weight with increasing age of the child and genetic variations in protein needs. Ordinarily, a child develops kwashiorkor only when several of these factors are interacting.

Our concept of the interrelationship between the development of kwashiorkor and marasmus is given schematically in Fig. 9. A normal child, indicated by the apex *N* of the triangle, when starved, would rapidly lose weight and pass through various degrees of malnutrition along the line *N–M*, to end in marasmus, designated as *M*. A child deprived of protein but given an abundance of calories would lose some weight in relation to age by not growing, but would move rapidly toward kwashiorkor along the line *N–K*.

Only in exceptional circumstances, however, would a child move smoothly along one of these two lines. Usually there is a long preliminary period of weight loss during which the child moves parallel to the line *N–M* until stress factors and dietary changes move him rapidly toward the base line *K–M*, which represents the continuous spectrum between marasmus and kwashior-

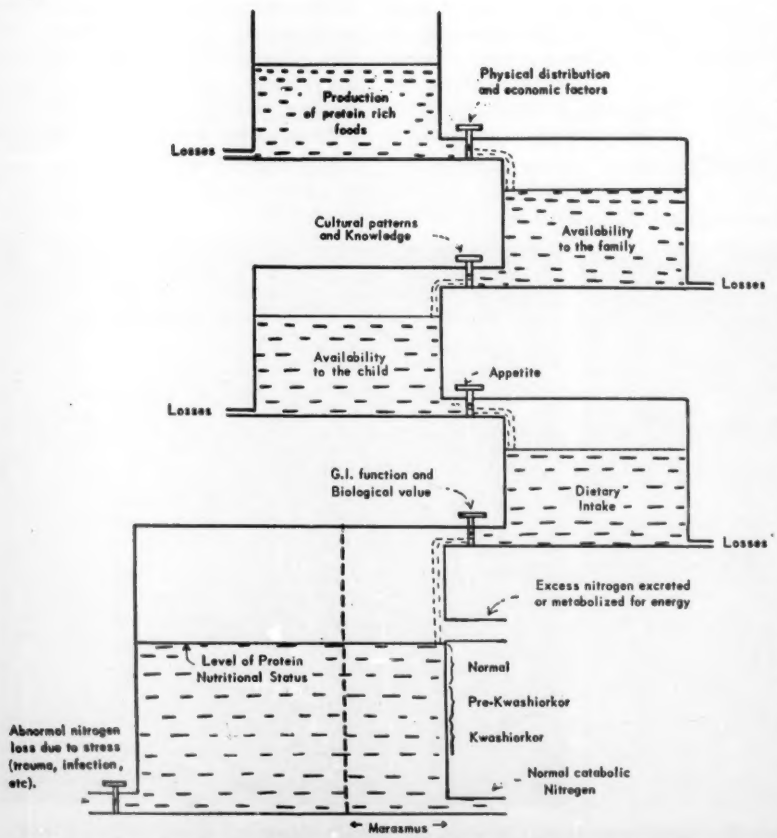

Fig. 8. Schematic representation of factors determining protein nutritional status.

kor illustrated in Fig. 8. Such a course is suggested by line *c* in Fig. 9.

Another common course, illustrated by line *b*, is that in which a child loses weight because of insufficient food and passes through an episode which moves him away from line *N–M* toward line *K–M*. He may then move again toward *M* in an intermediate zone parallel to line *N–M*, until a new episode results, this time, in moving him all the way to line *K–M*, with the resulting clinical appearance of marasmic kwashiorkor. Line *d* indicates that, as a child approaches marasmus, it is possible for him to move into the zone of kwashiorkor under stress, then move back toward the *N–M* line and display clinical symptoms of marasmus before an adverse change results in the superimposition of kwashiorkor.

All these lines could be taken equally well to represent the possible course of recovery, if they are followed in the reverse direction. Line *a* indicates that in the "sugar baby" type of kwashiorkor, the child, after recovery from the acute episode, is still somewhat below normal weight for his age.

On this basis, Fig. 10 indicates that it is possible to identify the clinical syndrome which the child presents at any point within this triangle. It can be seen that classification of malnutrition on a basis of percentage below standard weight—a system developed by some authors (*33*)—is useful under this scheme only in the limited area parallel to line *N–M*. The term *pre-kwashiorkor* is used to define those children who already have a few mild signs and symtoms of kwashiorkor and who should be considered on their way to developing the full-blown syndrome.

Treatment

The basic treatment of kwashiorkor is dietary. The child should be given a diet providing 3 to 5 grams of proteins of good biological value per kilogram of body weight per day. Cow's milk in any form is a convenient and effective source of protein. However, good results can be obtained with adequate combinations of proteins of vegetable origin (*34*) and even with mixtures of amino acids (*35*). Other foods should be progressively added so that by the second or third week of treatment the child is receiving a complete and varied diet, including fruits, vegetables, eggs, meat, and cereals, as well as milk.

Caloric intake should be high enough to insure good protein utilization. After the first few days of adaptation to the diet, an intake of about 150 calories

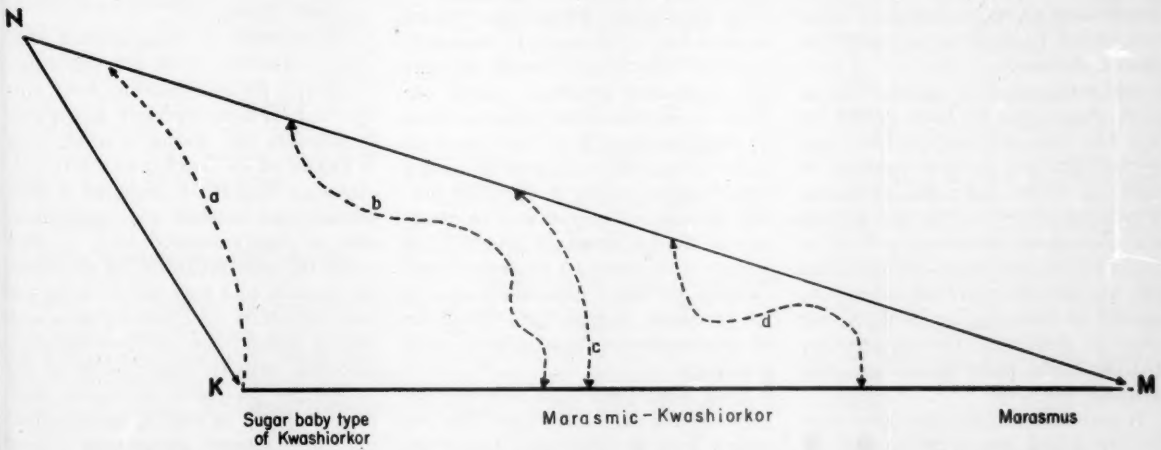

Fig. 9. Schematic representation of the development of the different types of protein malnutrition in children.

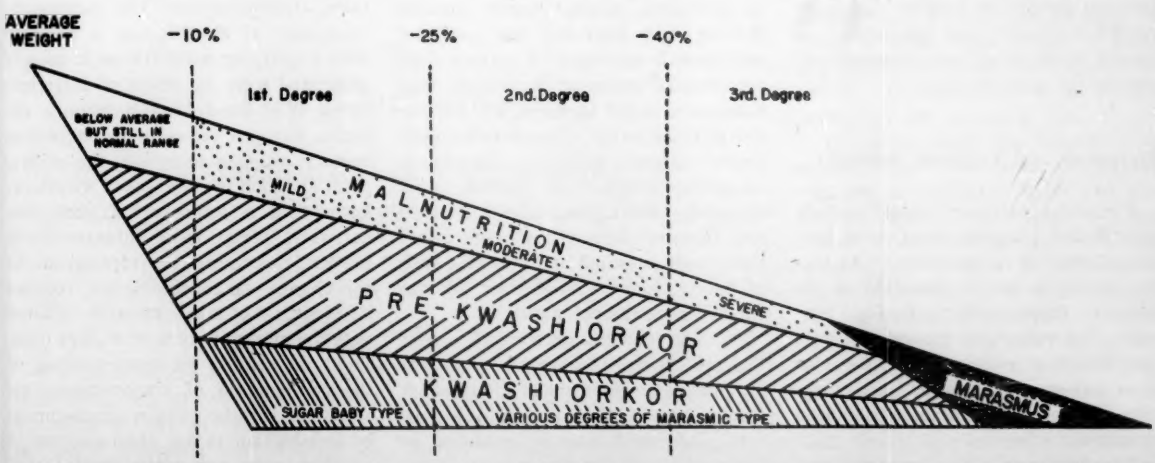

Fig. 10. Classification of the different types of protein malnutrition in children, based on the concept represented in Fig. 9. The classification developed by Gómez *et al.* (*33*) is shown by the dashed lines.

per kilogram of body weight, together with adequate protein, gives good results in most patients with kwashiorkor. In cases of marasmus or in very marasmatic cases of kwashiorkor, a higher intake of calories may be necessary after the initial phase of recovery.

It has been repeatedly demonstrated that, with good dietary treatment, there is no need for additional vitamins or minerals in most cases. Only when clinical or biochemical evidence of a severe deficiency of a specific nutrient is observed is it desirable to administer a vitamin or other specific nutrient. Children with megaloblastic or iron-deficiency anemias or ocular signs of vitamin A deficiency are among those requiring specific treatment.

Immediately after admission to the hospital and before initiation of the dietary treatment, measures should be taken to correct electrolyte imbalance in these children, particularly if clinical dehydration is present. Particular attention should be given to correcting potassium deficiency.

An antibiotic or a sulfonamide, or both, should also be given during the first few days of hospitalization, even if the child does not give evidence of infection. Severe infections, particularly bronchopneumonia, may develop with few clinical manifestations and be responsible for unexpected deaths during the first few days after admission. Obviously, if infection is found at any stage it should be treated promptly and effectively, since it interferes with adequate recovery.

It has also been found that good nursing and general care in the hospital, including adequate control of intake, isolation from infectious cases, cleanliness, frequent changes in position during the period of apathy, and affectionate attention at all times, are extremely important for good recovery.

Prevention and Unsolved Problems

Preventive measures should include prompt and adequate attention to individual cases of malnutrition, with special emphasis on the education of the parents; supplementary feeding programs for vulnerable groups, not only as a source of additional food but also as a means of education; and long-term projects to maintain a stabilized situation.

The first step in the long-term prevention of protein malnutrition in a country should be to increase, by all practical means, the availability of protein of good quality, particularly for the feeding of young children. Traditionally, providing foods of high protein quality has required an increase in the production of milk, cheese, meat, eggs, and fish. In most underdeveloped areas the means of increasing production of these foods are readily at hand but the cost is too high.

It now appears more practical to extend the usefulness of a given quantity of milk by adding it to vegetable mixtures (*36*), or to develop low-cost all-vegetable mixtures, such as Incaparina (*34, 37*), which have a protein content similar to that of milk and other products of animal origin. Also, advances in food technology have largely overcome the processing difficulties encountered in the past in making fish flour, meat meals, and soya preparations.

In areas where kwashiorkor occurs, mothers need to be taught to use locally available sources of protein, whether milk and dairy products, fish or fish flour, vegetable mixture, soya products or other legumes. It is also important that mothers learn to continue giving these protein sources to the child during episodes of illness. It may be necessary to combat erroneous beliefs which actually proscribe these foods for young children. Of major importance, also, is the processing and storage of foods so as to preserve or enhance their nutritive value.

Even when good food is consumed, several preventable conditions may interfere with its utilization. Heavy infestations of ascaris and other intestinal parasites, as well as frequent diarrhea of infectious origin, require specific therapy, and improved environmental sanitation is necessary to prevent their occurrence. Improved sanitation thus becomes a major factor in the prevention of kwashiorkor, along with immunization against smallpox, diphtheria, whooping cough, and tetanus, and (hopefully) also against measles. Prompt and effective therapy for acute infections, both intestinal and systemic, will, of course, help to limit their adverse effects on nutritional status.

Need for low-cost protein-rich foods: The prevention of kwashiorkor requires the further development of foods which furnish protein of good quality at low cost, and which can be produced in technically underdeveloped areas. Powdered skim milk is a partial solution for some regions, and fish flours and soya products may also be useful. It is evident, however, that the oilseeds are the most promising low-cost sources of protein for many areas.

The work of the Institute of Nutrition of Central America and Panama has shown that both cottonseed and sesame flours, if properly processed, can be combined with cereal grains in low-cost, palatable mixtures which have a protein content and quality comparable to that of foods of animal origin. The product, Incaparina, contains corn, sorghum, cottonseed flour, and *Torula* yeast and is already produced commercially in several Latin-American countries. Similar mixtures could be developed with local resources in countries where protein-containing foods of animal origin are in short supply or are too costly for low-income groups, and where neither cottonseed flour nor soya are available as cheap sources of vegetable protein.

Susceptibility of malnourished children to infection: While it is well established that children suffering from protein malnutrition are more susceptible to infection than normal children, little is known of the mechanisms involved. Antibody synthesis is impaired in protein-depleted animals and, apparently, also in protein-depleted man, but this is not the sole mechanism of resistance to infection and may not even be the most important one. Adverse effects of protein malnutrition on tissue integrity, leucocyte activity, and production of nonspecific protective substances have been proposed as possible mechanisms, but their relative importance is not known.

Mechanisms involved in the development of kwashiorkor: The sudden development of kwashiorkor in children with underlying malnutrition is usually associated with the stress of infection. While it is known that infections decrease nitrogen retention by increasing urinary nitrogen excretion, the critical point at which the changes of kwashiorkor set in is a matter of great uncertainty. Much more information is needed concerning the mechanism of this change and concerning the frequent development of kwashiorkor in children with the marasmic type of malnutrition. Until we acquire an understanding of the combination of circumstances responsible for the sudden development of kwashiorkor in one child and not in another under apparently similar conditions of dietary deficiency and other

stress, we will be handicapped in our efforts at diagnosis and prevention.

Regional variations: Although the basic characteristics of the kwashiorkor syndrome have been fairly well agreed upon, there remain baffling differences in the signs associated with the disease in different areas. While some of these differences may be due to genetic differences in skin pigmentation and in texture and color of hair, others seem more likely to be the result of variations in deficiencies of specific amino acids or of concomitant deficiencies of other nutrients. Elucidation of these differences should yield valuable information about the relationship of specific nutrients to those clinical signs which are inconstant accompaniments of the syndrome and about the interrelationships between a deficiency of protein and a deficiency of other nutrients. Particularly intriguing is the concept that kwashiorkor-producing diets differ in deficiencies of specific amino acids and that these differences account for some of the regional variations in clinical signs, even though a deficiency of any essential amino acid may produce the interference with protein anabolism which results in kwashiorkor.

Adverse Consequences and Sequelae

Thus far, attempts to demonstrate permanent sequelae from protein malnutrition alone have failed. There have been no sufficiently prolonged follow-up studies in which permanent sequelae have been sought. The effect of protein malnutrition in a child on the development of degenerative disease in an adult will, of course, be exceedingly difficult to determine. The recent demonstration of impaired intellectual capacity in malnourished children (*38*) is of tremendous importance and needs further investigation.

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Why Did Daedalus Leave?

Underdeveloped countries are aiding the developed by exporting one of their most precious commodities: talent.

Stevan Dedijer

The study of the social behavior of scientists is one of the least developed branches of one of the youngest of the social sciences: the sociology of science. Even the belles-lettres, as C. P. Snow recently pointed out, have practically ignored scientists. The rare and tenuous tracks back through time, marking an awareness of this type of human behavior, stop in Greek mythology. In the legend about Daedalus (*1*), the first mortal inventor in their mythology, the Greeks described the behavior of a man passionately devoted to what today would be called the solution of problems in applied research and completely free of any social and ethical norms.

Daedalus starts his career with murder: he kills from professional jealousy his colleague Talos and flees to the court of king Minos of Crete. There, by appropriate inventions, Daedalus solves a series of problems of questionable moral and political worth: he constructs a machine enabling Minos' wife to copulate with a bull, he devises the labyrinth so that Minos can hide the shameful monster born as the result of the previous invention, and finally he invents a device for

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solving the puzzle of the labyrinth, with the result that the subversive Athenian Theseus kills his employers' monster son and steals their daughter. Deciding suddenly to quit his post in Crete, and refused by Minos the permission to leave and the means of transport, Daedalus invents the flying machine (made famous by the death of Icarus) and takes off to a new post, in Sicily. Minos, who seems to have valued highly the services of Daedalus, sails with a fleet to find him and bring him back, and using the knowledge that the inventor cannot resist the challenge of a difficult problem, does find him. Daedalus then promptly solves the problem posed to him by his new employer: he constructs a bath such that when Minos pulls the shower handle he is scalded to death.

In this obviously tendentious legend one point remains obscure: if, as is evident, Minos did not want to lose him, why did Daedalus leave?

The migration—temporary and permanent—of individual researchers across state boundaries is as old as the history of science itself. And in puzzling, from today's perspective, over what prompted the flight of Daedalus from Crete, we can ask certain questions.

Did Daedalus leave because he felt that elsewhere he could work better on problems he was interested in, as scientists often feel today, and as for example the German Johannes Kepler felt in the year 1600 when he went to work in Prague with the Danish astronomer Tycho Brahe? Or did Daedalus emigrate because he felt about his colleagues in Crete just as the astronomer Ruggier Boshkovich felt about the scientific community in Rome in the 18th century, when he wrote home to Yugoslavia: "There is nothing more that I desire right now than to run away to Constantinople. For indeed, I expect that I shall find the Turks to be better than the Christians." Or did Daedalus leave because he felt that "it cannot be said that society provides good conditions for the proper growth of science" (*2*).

Such questions, bearing on the nature of the scientific work, on human relations existing within a scientific community, on the influence of social environment on creative research work, and on the effect of all these factors on the migration of scientists, are ceasing to be purely academic. For never before has there existed such an opportunity for the migration of Daedali, and never before have there been so many of them migrating across state boundaries as today. Until recently, the world scientific community was mostly concentrated in the more developed Western countries. Now the interaction of the three revolutions of our age—that of the underprivileged classes, that of the underprivileged nations, and the great scientific and technological revolution (*3*)—is causing, through the socially organized diffusion of science, a veritable explosion of the boundaries of the scientific community to include every corner of our globe. Almost every country today is helping to expand the world scientific community by efforts to detect and develop its own scientific talent. The Minoses of the world are beginning to count avariciously and to guard jealously their scientists and engineers and are becoming concerned over the propensity of these scientists and engineers to take off across the border.

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Daedali in Flight

This can be seen from a series of signals about Daedali leaving and Minoses trying to find them and bring them back, picked up in a sweep from the northwestern tip of Europe to the southeastern tip of Asia.

The Advisory Council on Scientific Policy of the British Government was the first to worry publicly, in its 1953–54 report, about "the loss of scientists abroad" and, in its 1956–57 report, about the "emigration of scientists and engineers."

Moving to the continent, we find a study group formed by the Science Committee of the North Atlantic Treaty Organization concerned in 1960: "It is noteworthy," states the committee, "that even some of the nations in Europe which are technically advanced and pay good salaries are steadily losing highly qualified young scientists through emigration. Some permanent exchange of scientists is inevitable and desirable: however, any country which suffers large and continuous losses should examine its policies with great care" (*4*).

In November 1959 I submitted to the newly formed Research Council of Yugoslavia a list of questions I suggested should be looked into. Under the leading "How many scientists are we losing abroad and why," I in part said: "The urgency of this problem is suggested among other [things] by the fact that a private enquiry reveals that in the last few years just our three nuclear institutes have lost some 20 scientists who are now working abroad."

From the home of the first Daedalus we hear of further flights: "The delegate from Switzerland said that his country has (and welcomes) about 300 Greek students and that the best of them do not want to return to Greece when they have qualified" (*5*).

Considering the state of science in the land of the Sphinx, a wise American says: "We should avoid weakening the intention of those of our visitors who come to study in the USA to return to teaching and research in the UAR. This is a delicate point and cannot be sharply defined, but I think that enticing UAR personnel in training in the USA to remain in the USA through offers of positions or other inducements would be bad" (*6*).

India became concerned with this problem a year or so after gaining independence and has recently been devoting serious attention to it. In July

1959, the Indian Council for Scientific and Industrial Research took practical measures in response to the following question: "There are also persons from India who are employed in the countries in which they have received postgraduate training in special fields. Is it possible to get them back and utilize their talent for furthering various projects under the national plan?" (*7*).

And from southeastern Asia, an international expert on the development of research and education wrote in November 1960: "too many of the able young men who have gone abroad for postgraduate study are remaining there or returning after a short period at home, because they have not received due recognition or have been unable to find a suitable position with adequate salary and facilities. In some countries, the loss of young qualified men has reached an alarming number. There is a growing discontent on the part of this young cadre of scientists and many governments are coming to the realization that means have to be found to put a stop to this drift of talent" (*8*).

Sociology of Science and Research Policy

The Daedalus of the Greek myth is a cleverly devised image of the ivory-tower inventor—a being all curiosity, all problem-formulating and problem-solving, and little else. At one time there was a strong tendency to consider science as the exclusive concern of such ivory-tower Daedali. Today, however, there is a fairly general agreement everywhere on two points: first, that "science like technology is a creation of societies, not races: its precepts and results are transmitted by social tradition" (*9*); and second, that society must provide good conditions for the growth of science through the appropriate set of decisions, called "research policy," whose one important component consists of "the social and political measures needed to make the scientific potential of a country both scientifically and socially productive" (*10*).

A research policy to be realistic has to be based on a thorough study of the interaction of science and society, which constitutes the field of the sociology of science. Yet, it can be safely said that, until quite recently, with few notable exceptions so far (*11*) the sociologists of science have been in general of little, if any, help to the policy makers on any of the principal components of the research policy. This is certainly true as regards the loss of the scientific talent through emigration. On the other hand, practical-minded decision makers are often inclined to find little that is useful in academic studies, which do not seem to have an immediate practical bearing on bothersome research-policy problems.

With the growth of efforts to make research become one division of labor within every society and a part of the culture of every people, and as the boundaries everywhere in the world become (let us hope) more open, one can expect that the migration of scientific talent will become a problem of international concern (it is surprising that it has not already become so, especially in the case of the new countries). The sociologists of science, by studying the flying Daedali as individuals of given mentalities doing a specific kind of work and migrating from one given professional environment and one given wider social environment to another, could not only advance their branch of inquiry but could also greatly aid the policy makers to find their way in the intricacies of the problem of migration of scientists, on both a national and an international scale.

Aiding the Developed Countries

The first and the obvious step in approaching this problem would be to attempt to collect, systematize, and classify (even roughly) on a world scale data on the migration of research talent. This could be done by giving, for each particular country, the number of emigrating or immigrating scientists and engineers, the direction of their flight, and their level of development.

In spite of the evident concern—public but even more private—of Minoses everywhere, very little of this is known, even for the most developed countries. Thus, from Britain we hear (*12*) that "there are no comprehensive statistics to show the extent of the movement," of scientists and engineers out of the United Kingdom, and from the United States (*13*) that "no one knows the precise number, or the nationality of foreign students who take up permanent residence in the United States."

In the absence of more precise data, for the purpose of this article, all countries could be roughly classified into three categories: (i) the current "sink" country for migrating research talent; (ii) the "sink-source" countries; and (iii) the current "source" countries.

And with respect to the level of development, the migrating research talent could be classified into: (i) the undetected scientific talent, leaving the country through general economic or political emigration; (ii) the raw talent (the undergraduate students); (iii) the semirealized talent (the graduate students); and (iv) the accomplished Daedali.

The United States seems to be the only sink country; scientists and engineers from all the countries of the presently open part of the world, especially from Europe, are emigrating to the United States, while there seems to be very little permanent migration from the United States.

Countries like Britain, Germany, France, and so on lose scientists, mostly to the United States, but gain them through immigration from other countries.

In general, countries just starting to develop in science are source countries. Scientists and engineers from such countries are emigrating not only to the United States, just as those from Britain, Italy and Germany are doing, but also to these latter countries. Generally, it is from new countries that the Daedali are migrating in one direction only: out.

And while the countries of the second category lose their scientists mainly on one—the postgraduate—level, the countries just starting in science lose them on all four levels of development to *all* the more advanced countries. In this way, one could say, the underdeveloped countries are aiding the developed ones by supplying them with one of their most precious commodities: creative talent.

Importing Research; Exporting Researchers

For a number of reasons, the problem of migration of research talent will be considered here from the point of view of source countries. This means that the very interesting ques-

tion of migration of scientists from "sink-source" countries, which have a tradition in science and as a rule a relatively vigorous research policy, will be considered only indirectly.

In the past, the underdeveloped regions of the world contributed to world science without having a scientific potential of their own. In this respect their position in relation to the world scientific community was somewhat similar to their position in the world commodity market: to both of them they exported raw and semifinished goods—in one case, agricultural and industrial products and in the other, their scientific talent. For example, of 12 scientists born in Yugoslavia and recently chosen in a survey by Yugoslav university professors as having contributed most to world science from the 16th to the middle of the 20th century, eight emigrated as boys and became scientists of world renown. Since 1945 my country has started a vigorous policy of developing its own resources and of creating for everyone an opportunity to improve his living conditions. As a result of this, the loss of the unidentified scientific talent through economic emigration can be said to have practically ceased. This kind of export of scientific talent can be expected to diminish in other cases to the degree that a vigorous policy of development is started, aiming to increase the well-being of the population.

But as such countries start to develop their research potential there is a growing tendency to lose a considerable proportion of it on all levels of its development: on undergraduate and graduate levels and on the level of full-fledged research. This seems to be a process parallel and opposite to that of the diffusion of scientific work from its birthplace in the West into social environments basically alien or unsuited organically to it.

This type of migration tends to occur, it seems, first of all on account of a trait of the research work itself: it can be learned only with difficulty from books. For "modern science is a local tradition and is not easily transmitted from one place to another . . . Scientific research . . . is an art; it is the art of making certain kinds of discoveries. Scientific research is taught by example" (*14*).

In my country, Yugoslavia, the number of university students today is at least five times greater than in 1940 and the annual university expenditure has increased even more. Contrary to the situation for some other countries, the number of Yugoslav undergraduates studying abroad is, for a number of reasons, extremely small. Yet today the university, as a social institution whose function is to develop creative talent, among its many increasingly modern traits still has many traits characteristic of the decidedly undeveloped country that was old Yugoslavia. One of them is that there is no tradition of research at the university; during the four years of study the undergraduate student as a rule still has no contact whatsoever with research or with problem-solving in general. Graduate study, the level at which a young man's research mettle is first seriously tried, is just being organized now. And after graduating, those going to the research institutes (those remaining at the university still have little opportunity for research) suddenly face the question, often heard and repeated, "How does one do research?" since up to that time they have had almost no contact with a practitioner of "the art of scientific work." So a new country without science has to import it; it has to send its promising—usually its most promising—research talent abroad, hoping that upon returning these men will act as local centers of diffusion of the art of research. That is why it is not unusual in new countries to find institutes almost empty of researchers: they are abroad learning the art.

The countries with a developed research have opened their doors to thousands of such young graduate and undergraduate students. For example, in the United States there were in 1959 over 65,000 foreign students, 18,000 of them graduate students; in the United Kingdom the figures are 11,047 and 4286; in Austria and Switzerland one-third of the total student body consists of foreigners. Most of these students are working in natural sciences, medicine, and engineering, and the majority of them come from what we called "source" countries. Quite a number of such countries have more students abroad than in their own institutions of higher learning.

And what happens is that many talented (often the most talented) citizens of, let us say, Zonia, who have gone abroad to import the art of science or engineering, become scientists or engineers and in the process cease to be Zonians; they do not return home. When the impact of such losses begins to impress the Minoses of Zonia, they begin to grumble: the open door is an open door of a trap for our Daedali (*15*).

Responsible people in the United States, the principal host country, have shown concern over this problem: "US Government agencies believe that two basic objectives of the exchange program are frustrated when students emigrate to the USA. They are the opportunity to promote international amity, which is considered the primary purpose of educational exchange, and the opportunity to help other countries' social and economic progress, which is also considered an important goal" (*13*). Such people are trying to find "what can be done on the US side to encourage students to return home?" (*16*).

There are indications that other host countries are beginning to ask such questions. The problem of the emigration not only of students but also of experienced scientists and engineers from the source countries is beginning to be considered on an interstate level. International agencies are beginning to discuss it in committees. In spite of this encouraging trend, realists must recognize that one can hardly expect government agencies, let alone private firms and institutions, "not to entice" the talented foreign scientists, young or mature, who hope to be enticed. In the end, the main burden of stopping the critical loss through emigration of scientific talent on all levels of its development falls on the Minoses of the countries from which the Daedali are emigrating; it is principally they who must bear the responsibility for transforming their source country into a source-sink country.

Information Needed for Action

In order to make the appropriate decisions, the responsible decision makers must have information on the following points: (i) How much research talent have they lost and are they losing on all levels? (ii) What has been found elsewhere about why scientists and engineers leave? (iii) Why have their own Daedali left; in other words, what factors in the domestic scientific and social environment tend to make them a source and not a source-sink country?

To obtain information about the first point it is not enough to count the number of emigrating students or full-fledged researchers. In the final sum one must include not only the quality of the research talent of the individual emigrants but also their qualities as social beings acting within a given scientific and a wider social environment. One must estimate their quality as leaders and teachers of research and science, the strength and the effectiveness (actual or potential) of their participation in the interaction between science and society—for example, as administrators of science or as persons having the not easily found ability to communicate to the decision makers the information needed for an effective research policy.

The decision to emigrate or stay at home is the resultant of attractions and repulsions acting on an individual from two professional and social environments; it is a choice made, through the free will of individuals, between two sets of alternatives. This is seen, for example, in the following case. Recently, a prominent scientist from a source country wrote: "The conditions for science in my country are unsupportable. Everything here tells me that both as an individual researcher and as a social being I am not needed nor wanted," and then he took off for the United States, where, as we saw, a prominent group of scientists proclaimed, "It cannot be said that society provides good conditions for the proper growth of science."

The number of researchers and engineers who have left the sink-source and the current source countries in the past ten years runs, probably, into thousands. But it seems that no exhaustive study has been published about even a small sample of this number from which one could define roughly the principal motives for emigration that influence individuals as private persons, as professionals, and as socio-political beings. All one can do at this stage is to draw up from the existing sources a list of the factors said to be influential in the decisions of individuals to emigrate. This list would include: salary; material standard of living; status in the scientific community; opportunity to advance professionally on the basis of ability; ease of obtaining the means for research; degree of development of the scientific branch the scientist has been trained in or wants to work in; status in the social community; and finally, a number of factors lumped under the general heading of socio-political factors.

The relative weight of these and other factors influencing the decision to emigrate has not as yet been published, even for a small number of cases. But from all the information available one may hazard a guess that the higher salaries offered, the higher standard of living abroad, and the purely political reasons (except under extreme circumstances) perhaps do not play as decisive a role as some decision makers from source countries are inclined to think without full examination.

In approaching studiously this problem one must not forget that this choice made by an individual one way or another is always the result of an intense inner struggle, for it involves cutting oneself off from innumerable ties strongly binding one to a particular social environment and going into a new and an alien one. Kepler, for example, deciding not to emigrate in 1615 wrote: "Am I to go overseas [to England], where Wotton invites me? I a German? I who love the firm continent and who shrink at the idea of an island in the narrow boundaries of which I feel the dangers in advance" (*17*). In 1959 one scientist who emigrated wrote: "I decided to leave the country where I was born, to which I am tied by all the joys and sufferings, by all the failures and successes of my 45 years of life. It was the most difficult decision I had to make."

The Macro and the Atomic Approach in the Sociology of Science

We shall assume that the decision makers from the source countries are aware of the problem of emigration of scientists and that they desire the necessary information to make them a source-sink country. This is quite an assumption. For, first of all, very often in such countries the ability of many of the best-intentioned decision makers to supply initiative for the collection and the evaluation of information and to act effectively upon the data meaningful for their field of responsibility is limited by their educational background and the environment to which they belong. To realize how bold this assumption is, one has only to see how little study preceded some of the big government decisions with respect to science in some source countries.

In order to obtain the necessary information, the decision makers will have to turn for help to the sociology of science. And here we come against the attitude of one category of decision makers from some source countries toward the social sciences in general and the scientific study of the micro-social relations of their society in particular.

The process of developing a country consists to a large degree in importing and grafting modern civilization onto an alien and a resisting social environment. The greater the social urge and the will to develop, the higher the goal, the shorter the time for reaching it, and the stronger the pressure of the past upon the living (including the decision makers), the more painful is the process for everyone involved. Under the best of circumstances the decision makers of such countries are human beings working under enormous pressures, which unfortunately are rarely described and are difficult to imagine from the outside. Man being an ideological animal, the pressure to get things done inclines such decision makers to accept the action philosophy —that rapid results can be obtained at the cost of the most abundant available commodity: human beings. This ideology readily finds its logical expression in the exclusive and dogmatic acceptance of theories of society which deal with man only in macro dimension, only as "masses" moving under the action of forces and according to the "laws of motion" of human matter. This macro approach treats man in bulk, in "zero approximation," as a biological and an economic being, neglecting most of his other needs and the fact that he is motivated "not by bread alone." This attitude toward the social sciences is likely to be prominent especially in the first, the hardest, phases of rapid development.

The Ecology of Research

This macro approach—believed by many Minoses to be sufficient—excludes the other necessary theoretical guide for action: the atomic approach, which describes society as composed of individuals and groups of individuals doing specialized kinds of work and having a variety of inherited and acquired aspirations, mentalities, and

attitudes and communicating and reacting with other individuals or groups, the totality of these interactions forming a given social environment. Whatever is the value of the macro social theories, the atomic approach is essential in considering problems of interaction of science and society. For masses never invented a machine or produced a scientific theory. Everything in science is the product of individual social beings; and the loss of one single talented Daedalus can set back a scientific institution for years.

When, either through social sciences or through the observation of the outside world, the decision makers inclined to hold macro social theories become aware of the necessity of importing and grafting research onto their own society, they are likely to be guided in their decisions by the formula:

Effective research =
[in order of importance]
machines +
buildings +
money +
research program tied closely to
political and economic goals +
a set of formal research institutions +
a quantity of problem-solving Daedali.

Through painful experience and immeasurable waste they discover that this formula does not fit the facts, that there is operating in it a hidden parameter. This is what in the developed countries is called "scientific tradition." One speaks of the scientific tradition of a scientific institution, of the whole scientific community, or in the relations between the decision makers and science. Both the history and the sociology of science have neglected the study of *how* and under what micro social conditions scientists create their work and transmit the art of research to the young talents of the new generation. Scientific tradition developed gradually in the West, unobserved and almost unfelt. It could be defined as a communication of experience by other than written means. Until recently it is only in literature, and very rarely at that, that we find mentioned the cost in men of this "rugged individualism" kind of development of social conditions for science. Thus, in his novel *The Search*, C. P. Snow has one of his characters say: "And so I had to draw young men, and having got them, see that they were not wasted. That, I thought, was where I ought to be useful: for from all the laboratories I knew, the number of men thrown away by negligence, by incompetence, by sheer ignorance of the fact that there are differences between young men, would be enough to stock a reasonable scientific society in South America. . . . There must be a certain amount of trial and error, however, and one cannot expect a career in science or anything else to be adjusted with immaculate precision. But there is altogether too little trial and too much error. Luck must play a big part; but that does not seem a good reason for letting it decide altogether."

Must the source countries develop tradition purely by "trying and erring" with their scientific talent—young and old? In the world of today, in a world becoming more and more open and where there is more and more science, this is becoming impossible.

The process of developing a country, the process from no tradition in science to a tradition in science, is very painful for scientists also. Most of them, trained abroad or not, work in a social environment which is alien to science and research, and most of them find themselves to be, as a prominent physicist put it, overdeveloped scientists in underdeveloped societies. For no social institution around them—the institute, the university, the scientific community, and the decision makers—"has a tradition for science." This lack of the proper social environment or tradition acts upon researchers as a strong pressure outwards. The flight of Daedali from source countries is only one measure of the painfulness of the process; it is only one symptom of the relatively unsound social conditions for science. For it must be kept in mind that for every Daedalus who is willing or able to fly away there are many other grounded Daedali who stagnate, succumb, and are destroyed as research talent by the unfavorable social conditions. The novel of the Soviet writer Dudintsev, *Not by Bread Alone* (not to look for further evidence from the countries which until recently grounded their Daedali) speaks eloquently of that.

As the world becomes more open and as, one hopes, peaceful coexistence becomes a reality, the Minoses of the source countries can less and less afford to ignore the missing factor of science tradition in their formula. They will have, so to speak, to manufacture rapidly this tradition. To develop an effective research potential they must alter the local environment in the direction of making it, through conscious efforts, by policy measures, favorable to scientific work, which up to now, has not had a part in the culture of their society. To be able to do this, the wise source-country Minoses will have to initiate the study of the relation of the existing micro and macro social environment and the research work. This study—which can be called the ecology of research—can contribute greatly to the transformation of an environment alien to science to one attractive for the work of individual Daedali.

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5. "Annual Review of Progress in the Field of Highly Qualified Scientific and Technical Personnel (1958–1959), Greece," *Organisation for European Economic Co-operation Rept.* (Paris, 1960).
6. S. K. Allison, *Bull. Atomic Scientists* **16**, 318 (1960).
7. *J. Industrial and Sci. Research* (July 1959).
8. W. J. Ellis, "Survey of Some of the Problems of Science Teaching in South and South East Asia" (UNESCO, Paris, 1960).
9. G. Childe, *The Prehistory of European Society* (Penguin, London, 1958).
10. S. Dedijer, *Nature* **187**, 458 (1960).
11. One notable exception is the vigorous research policy of the Soviet Union since 1917. This can be attributed to a considerable degree to the influence of the views of two prominent sociologists of science, Marx and Engels.
12. T. Raison, *New Scientist* **8**, 278 (1960).
13. *The Foreign Student: Exchangee or Immigrant?* (Committee on Educational Interchange Policy, New York, 1958).
14. M. Polanyi, *The Logic of Liberty* (Univ. of Chicago Press, Chicago, Ill., 1951).
15. One prominent Minos privately claimed that the trap is baited—with *women!*
16. *African Students in the USA* (Committee on Educational Interchange Policy, New York, 1960).
17. M. Caspar, quoted by A. Koestler [*The Sleepwalkers* (Hutchinson, London, 1959), p. 402.]

Science in the News

The Education Bills. A Few Items of Controversy: Parochial Schools; the Yellin Case; Teaching Communism

The Administration's public school bill, as of the beginning of this week, had nowhere to go but up. At the beginning of the month the path seemed clear (and so it was erroneously reported here) for the bill to come before the House with the fight over money for private (that is, essentially for parochial) schools muffled as much as could be expected. The bill would have had the additional advantage that consideration would come just after the President's return from his round of meetings with Macmillan, De Gaulle, and Khrushchev, a time when the House would be especially leery of handing the President his first major defeat.

The problem of the Rules Committee had been, it was thought, taken care of last January. The deadlock between six liberal Democrats and a conservative bloc of two Southern Democrats and four conservative Republicans had been broken by allowing the Republican leadership, stoutly conservative, to add another member to its liking, while the Democrats added two liberals. The liberals now had an 8-to-7 majority, and the Democratic leadership had, so it seemed, control of the committee. Yet, for what at the time seemed inexplicable reasons, the leadership put off asking the committee for the necessary rule governing the terms of debate on the bill. The reason for the delay, it turned out, was that the Democratic leadership did not, after all, have a majority. The liberal bloc on the committee included two Catholics, and more important, Catholics representing predominantly Catholic districts (one of the leaders on the Catholic side of the private school controversy, Representative Zelenko of New York, is Jewish, but he too represents a predominantly Catholic district). The two Catholics were prepared to vote with the conservative seven to refuse a rule to the school bill, and they threatened to continue to oppose a rule for the bill until the Education and Labor Committee had voted out a version of the National Defense Education Act, which is up for renewal this year, that would include a loan program for private schools.

Last week, the threats became fact, and the committee voted 9 to 6 against considering a rule for the school bill until the NDEA extension had been reported out of committee. Speaker Sam Rayburn was reported to have told the President that the school bill looked "dead as slavery," and Congressman Adam Clayton Powell, chairman of the Education and Labor Committee, called a press conference to announce that things looked very bleak indeed and that it was up to "someone higher up [the President, of course] to blow the whistle."

Powell went back to work with his committee to try to get out an NDEA extension satisfactory to the Catholics, but whether he succeeds or not the school bill has taken a bad blow.

The Catholic position is that nearly 15 percent of school age children in the country attend parochial schools, saving their non-Catholic fellow citizens a large part of the immense amount of money that would otherwise be needed to take care of the added enrollment that would result if the parochial schools closed. If the federal government is going in heavily for aid to schools, and the Administration bill implies a permanent and very substantial program, the Catholic view is that some consideration should be given to the 15 percent of the students who do not attend public schools. It is generally agreed that grants would be unconstitutional. But long-term, low-interest loans, although costing the federal government nothing, would be a substantial help to the parochial schools, probably would not be held unconstitutional by the Supreme Court, and seem to the Catholics to be a modest and reasonable compromise.

The Catholic demands, then, are by no means entirely unreasonable. The Administration's efforts to go at least part way in accommodating them are not, in themselves, unusual. It is a commonplace situation in politics, whether at the level of the departmental factions in a university or at the highest level of international politics, for *A* to make certain demands on *B* as the price for supporting something that *B* wants. The parochial school bloc wants at least a fighting chance to get a bill incorporating loans (not grants) through Congress as the price for supporting the Administration's large-scale grant program for the public schools. This would involve getting a loan bill through committees and to the floor of both Houses of Congress. If all this had been done quietly, and the issue involved had not been one so capable of arousing strong passions, then the maneuvering on the school bill would have been essentially no different from that which paves the way for the passage (or defeat) of any piece of controversial legislation. But as with a magician's performance, for the maneuvering to show spoils the performance.

President's Role

The maneuvering on the school bill, which became a matter of public record with the vote in the Rules Committee, has reached a point where it has become distasteful to everybody, and unless counteracted it would assuredly cost enough votes among the wavering members who hold the balance of power to defeat the bill. The Administration has not given up. Abraham Ribicoff, the Secretary of Health, Education and Welfare, cancelled his scheduled appearance at the governors' conference in Hawaii this week to be on hand in Washington to help on the bill. Kennedy sent a message to the National Education Association convention assuring them that he still saw "every reason to believe" that he would sign a school aid bill into law "before the summer is out." But the chances of passage, more than ever, depend on the President.

What the situation seems to call for, on the part of supporters of the bill, is to let things lie for a bit, until the passions generated last week can cool off, and then to try to get off to a fresh start just before bringing the bill be-

fore the House. The most effective fresh start, of course, would take the form of a Presidential address over television. But no announcement can be expected on this, if it is to happen, until a day or two before the event, not only because the President would not commit himself to using this last resort unless it had become clear that nothing else would do, but because in any case it would be bad tactics to telegraph the punch by announcing it prematurely.

National Defense Education Act

Meanwhile, although the NDEA extension has been getting attention mostly because of the effort to attach an amendment for private school loans, the bill, of course, is an important one in its own right.

The Administration draft, except for the addition of the special loan program for private schools, is likely to be reported out of the House and Senate committees substantially unchanged. It will put NDEA on a permanent basis, with a yearly appropriation limit of about double the $250 million that is now being spent. The present act provides support for secondary school teaching in mathematics, science, and foreign languages, as well as the better-known programs of loans for college students and fellowships for graduate students. Kennedy asked that English and physical fitness be added to the secondary school subject areas, with the provision that money for physical fitness could not be spent on a facility for holding athletics contests to which admission would be charged. It appeared that English would be added, but there was substantial opposition to the physical fitness program.

Another fellowship program, this time the engineering and science fellowships set up in the National Science Foundation Act, was also in the news.

The Yellin case, described in the editorial at the front of this issue, brought a Congressional demand for changes in the National Science Foundation Act to prevent the award of a grant to a student of questionable loyalty. A bill produced by Overton Brooks, chairman of the House Science and Astronautics Committee, writes into the law the interpretation of "ability" which the Foundation used as part of the basis for rescinding Yellin's grant. In effect, it provides that intellectual competence will not be the sole criterion for deciding who will get a fellowship, but that in assessing a student's ability the Foundation should also consider the student's motivation and his loyalty to democratic principles. The bill appeared extremely likely to pass.

The question of communism also got into the discussion of the NDEA, but in a way which aroused nothing like the fuss the Yellin case provoked.

Senator Goldwater called a press conference to announce that he would offer an amendment to add to the bill support for studies concerned with the threat of communism. Goldwater criticized the Administration for trying to add support for English and physical fitness at the same time it was trying to delete the provision requiring a non-communist affidavit from applicants for the student loans provided in the act. "It is difficult for me to see," Goldwater said, "how any intelligent person can genuinely believe that improving and expanding educational courses in English and physical fitness is more essential to the national defense than a provision designed to protect the American taxpayer against having his tax money used to benefit the enemies of the Nation."

Goldwater said he was opposed to the bill, as he was opposed to all federal aid to education, but that since it was certain to pass anyway he would vote for it himself if the threat of communism was added to the subject areas to be supported. But there was not much likelihood that the amendment would pass, for the way in which one defines the precise nature of the communist threat implies in large measure what should be done to meet the threat. The result is that it would be extremely difficult to design a course in the threat of communism that would not strike some substantial group as a gross, and perhaps treasonable, misuse of public money.

Satellite Communications

At the beginning of the week the White House took its first formal notice of the imminent need to lay out a policy for the development of a worldwide satellite communications system. It made public a letter from the President to Vice President Johnson requesting Johnson, in his role as chairman of the Federal Space Council, to "make the necessary studies and Government-wide policy recommendations for bringing into optimum use at the earliest practicable time operational communications satellites. The letter, dated 15 June, was made public last Sunday, the 25th.

Some of the policy problems this involves were reported here a few weeks ago (*Science*, 9 June). The economics of the situation was discussed in an article in *Science* (16 June) by William Mechling, of the Rand Corporation. The most politically touchy problem is the very basic one of the extent of federal financing and perhaps ownership that will be involved.

The President asked for recommendations of the "nature and diversity of ownership and operation" of the system. The President said that in making these recommendations "public-interest objectives should be given the highest priority." Nothing was said of any preference for private, rather than public, ownership. The release of the letter thus announced, in effect, that the new Administration feels no commitment to carry on the policy laid down in the closing days of the Eisenhower Administration that the satellite system should be developed by private industry.

Japanese Agreement

The Prime Minister of Japan, Hayato Ikeda, was in Washington last week, and his visit, primarily concerned with trade and tariff matters, provided the occasion for announcing what the State Department hopes will be the most elaborate cultural and scientific agreement we have set up with any country. Earlier in the month the Department negotiated a settlement of the debts Japan owed the U.S. for occupation costs after the war. The bulk of the $490 million settlement has been set aside for aid to underdeveloped Asian countries, but $25 million will be used to finance a program of cultural and scientific cooperation. The announcement last week simply made public the decision to set up binational committees, which will work out the details of the program. But the program the Department has in mind will involve financing joint projects to be worked on by Japanese and American scholars and scientists, thus going beyond the usual exchange of visits associated with such agreements. If the program works well it will presumably be used as a pattern for similar arrangements with other nations.—H.M.

Communist and U.S. Exchanges

The Department of State will begin negotiations next month with the Russians for a new and more ambitious exchange agreement to succeed the present one, which expires the end of this year. A Department spokesman called the present educational, cultural, and scientific exchange program "elementary." He said the hope is that the new agreement for 1962–63 will extend the term of exchange visits and expand the subject areas as well as increase the numbers of persons involved.

The exchanges began in 1958. Soviet interest has been primarily in scientific and technical fields and in cultural exchanges, and these have proceeded smoothly.

To date, Soviet scientists have attended 12 conferences of international organizations here, while Americans have attended six such conferences in the U.S.S.R. In addition, there was a special and separate exchange of delegations in the fields of high-energy physics and controlled thermonuclear reactions. About 300 Soviet scientists are scheduled to attend meetings in the United States next month. In August, 800 American biochemists will attend the international meeting on biochemistry in Moscow. There also have been several exchanges, arranged with little or no difficulty, in industry, agriculture, medicine and public health, and economics.

But Russian distinterest and even aversion have been plain when it came to exchanges in areas involving political and social ideas. In these areas the program has been marked by friction. This has prevented, thus far, an agreement for a reasonably free exchange of books, magazines, or newspapers. The Russians have restricted the circulation of the U.S. publication *Amerika* to 52,000. No restriction is placed, in the United States, on the circulation of the Soviet magazine *USSR*. There has been no exchange of professors, as called for in the agreement. Such an exchange would involve teaching visits of an academic year or longer. The Russians prefer short-term exchanges. Where there have been educational exchanges—to study language teaching, technical education, and art—they have not exceeded 4 weeks. The Russians also have opposed U.S. exhibits in the U.S.S.R., mainly by making the cost prohibitive. Recently, however, after long delay, arrangements were made for three American traveling exhibits to visit seven cities. These will be exhibits on plastics, medicine, and transportation, again emphasizing the Soviet interest in technical, industrial, and scientific information. Television and radio are areas that also reflect Soviet reluctance to be exposed to American ideas.

Exchanges with communist countries other than the U.S.S.R. have been extremely limited, with the exception of Poland, where the exchanges, particularly those involving political and social ideas, have been markedly freer than those with the Soviet Union. The magazines *Ameryka* and *Poland* are on sale in the respective countries without limit. Poland has received a large number of American motion pictures, television films, books and periodicals, and has imposed very little censorship. And since 1957, Voice of America programs have been received in Poland twice daily without jamming or interference.

The Polish program, again in sharp contrast with the U.S.S.R.'s, has included many academic visits of a year or more to this country by Poles, most of them under private auspices. Last year over 100 Poles were in the United States for study; and since 1956 more than 1000 have come here, over 200 under Ford and Rockefeller Foundation grants. Ford grants have been primarily in the humanities, but with a growing emphasis on science. To date there have been far more Polish visits to this country than American visits to Poland. Recently completed negotiations for exchanges with Poland have expanded the program both ways.

As to other iron curtain countries, during 1960 Czechoslovak specialists attended 15 conferences in this country. Americans attended 11 conferences in Czechoslovakia. Only a very few Czechoslovak scientists came to this country last year, all under private auspices.

There has been no exchange agreement with Hungary since 1956, although there have been a limited number of private exchanges of individual visits, including teachers and scientists. This is also true of Bulgaria. However, since diplomatic missions were reopened last year, the prospects appear favorable for increased exchange activities.

On 9 December 1960, negotiations began for a limited U.S.-Rumanian exchange program for 1961–62, in education, science, industry, arts, publications, radio-television, exhibits, motion pictures, and sports. Two American graduate students are in Bucharest and four Rumanian students are at American universities for the 1960–61 academic year.

Cost of Space Exploration

Last week, Senator Warren G. Magnuson (D.-Wash.), chairman of a Senate Appropriations Subcommittee, told officials from the National Aeronautics and Space Administration (NASA) that "a lot of missionary work" had to be done with both the American public and Congress before a decision could be reached on the multibillion dollar request for getting a man on the moon.

Present estimates are that it will cost the United States $20 billion and take 10 years to put a man on the moon. As a recent Gallup poll made clear, the public is not convinced that getting a man there is worth this investment, and they have been letting their Senators and Congressmen know it.

Hugh L. Dryden, deputy director of NASA, has asked the subcommittee for an extra $549 million this year to initiate the accelerated space program urged by Kennedy to get to the moon ahead of the Russians. Dryden said that the space effort would yield new technological developments that would strengthen the nation's economy by providing jobs and new industries.

The results of materials research in ceramics, metals, and plastics for use in space are now finding their way into industry and to the public. The values of new fuels, new methods of power generation, and supersonic transportation are clear. By studying the effects of radiation in outer space, better methods may be discovered to protect man on earth from the possible risks involved in advancing industrial nuclear power. These are benefits that the average man can understand, but they are not what the scientist is aiming for in his reach toward the moon.

Homer E. Newell, deputy director of NASA's office of Space Flight Programs, last week listed the scientific goals in an address before a meeting of AMVETS in Washington. "Out of the scientific research will come knowledge; knowledge about the universe and its laws; knowledge about the earth upon which we live, its atmosphere, the sun, and the sun's influence on the earth; knowledge about physical life, its origins and fundamental nature. . . . Past experience has shown that the most important benefits of our research are probably unforeseen."

Announcements

More than $108 million—half of it federal funds—has been used during the two fiscal years since passage of the National Defense Education Act to improve the teaching of science and mathematics in the public elementary and secondary schools. The U.S. Office of Education announced that states have approved 56,545 projects, ranging from less than $100 to more than $50,000, involving science and mathematics, including equipment and minor remodeling of classrooms and laboratories. As a result of this combined federal, state, and local effort, advanced concepts of mathematics are being introduced at earlier grade levels, and high schools are adding courses in mathematics. There is greater emphasis on laboratory work, more science instruction is provided in the elementary schools, and advanced chemistry and physics courses are being added to high school curriculums. Many states report that enrollments in science and mathematics have risen, in some schools, 40 to 50 percent.

A recent AAAS study, sponsored by the National Science Foundation, proposes that science education should begin in kindergarten, as part of a major program to effect improvements in science and mathematics instruction in all grades through junior high school [*Science* **133**, 2019 (23 June 1961)].

Research groups in **aviation medicine, technology, electronics**, and **law** have recently been established by the Santos Dumont Foundation in Brazil. Institutions or individuals specializing in these fields are invited to write the foundation. (Ove Schirm, Fundação Santos Dumont, São Paulo, Brazil)

The **Bibliography of Temperature Measurement**, covering the period from January 1953 to June 1960, lists 500 references on temperature measurement, calibration of instruments, and theories supporting measurement techniques. [Superintendent of Documents, U.S. Government Printing Office, Washington 25, D.C. (National Bureau of Standards Monograph No. 27) $0.15]

The third edition of the **National Institutes of Health Scientific Directory and Annual Bibliography** is available to research workers in the biomedical sciences. The publication lists 1600 scientific and technical papers deriving from the NIH program of direct research—laboratory and clinical—during 1960. The subject index reflects the scope of NIH research and provides reference to major and subordinate research areas. (Public Information Section, Office of Research Information, National Institutes of Health, Bethesda, Md.)

The **Placement Service of the Biophysical Society** has listings of positions open in several areas of biophysics. It also has names of candidates for positions in these fields. The service is free, and membership in the society is not required for registration. (Biophysical Society Placement Service, Box 668, Frederick, Md.)

A **collection of articles** translated from *Advances in Physical Sciences*, a journal of the Academy of Sciences of the U.S.S.R, has been published by the Department of Commerce. Included in the volume are a discussion of the origin of cosmic rays, a report on semiconductor bolometers, and a Soviet scientist's interpretation of quantum mechanics. [Office of Technical Services, Business and Defense Services Administration, U.S. Department of Commerce, Washington 25, D.C. (AEC-tr-3972, $7)]

The International Commission on **Zoological Nomenclature**, London, has issued a notice relative to the proposed use of its plenary powers in the matter of validation or suppression of certain generic and specific names and designation of certain type species. Full details are given in the 16 June issue of the *Bulletin of Zoological Nomenclature*. Zoologists who wish to comment on any of the cases should do so in writing, in duplicate, prior to *16 December*. (Secretary, International Commission on Zoological Nomenclature, c/o British Museum, Cromwell Rd., London, S.W.7)

Meeting Notes

A conference on **internal friction** will be held 10–11 July at Cornell University. The meeting, sponsored jointly by the Defense Department's Advanced Research Projects Agency and the Atomic Energy Commission, will include sessions on pinning of dislocations by point defects; low-temperature peaks in deformed materials; phenomena involving diffusion-type motion of point defects; and very-high-frequency techniques. (Paul Leurgans, Materials Science Center, Thurston Hall, Cornell University, Ithaca, N.Y.)

A 2-day conference on **radio spectroscopy of solids**, sponsored by the British Radio Spectroscopy Group and the Institute of Physics and Physical Society, will be held 21–22 September at the University College of North Wales, Bangor. (Administration Assistant, Institute of Physics and the Physical Society, 47 Belgrave Sq., London, S.W.1)

Joint conferences on **nuclear reactor chemistry** and **analytical chemistry in nuclear reactor technology**, sponsored by Oak Ridge National Laboratory, will be held in Gatlinburg, Tennessee, 10–12 October. Deadline for submission of abstracts is *15 July*. [W. R. Grimes (for nuclear reactor chemistry) or C. D. Susano (for analytical chemistry), Oak Ridge National Laboratory, P.O. Box X, Oak Ridge, Tenn.]

Grants, Fellowships, and Awards

Organizations sponsoring short courses in science at an advanced level may be eligible for financial support under the **NATO Advanced Study Institute Program**. Courses may be in any of the sciences and should last for 2 weeks or longer, with participants drawn from several countries. The courses may include experimental work. Deadline: *1 December*. (Scientific Affairs Division, NATO, Place du Maréchal de Lattre de Tassigny, Paris 16e, France)

The Selby fellowship, recently established by the Australian Academy of Science, is to be awarded to a young scholar for work in **physical or biological science** at a university or research institution in Australia. Applicants should be under 30 years of age on 1 July of the year in which their applications are received; they should hold a Ph.D. degree or its equivalent and must have had preliminary research experience in a country other than Australia. The fellowship will not normally be awarded to anyone who has previously held a senior research award. The recipient will devote full time to research. Deadline: *30 July*. (Assistant Secretary, Australian Academy of Science, Gordon St., Canberra City, Australia)

Scientists in the News

M. Carl Walske, theoretical physicist serving as a member of the U.S. delegation to the Geneva test-ban conference since 1959, has been appointed scientific representative of the Atomic Energy Commission in London. He succeeds **Louis B. Werner**, who has accepted the position of vice president of Hazelton Nuclear Science Corporation, Palo Alto, California.

John D. Dwyer, director of the department of biology at St. Louis University, has received the J. Henri Fabre award from the French Government for his studies of French tropical plants.

Martin Barr, professor of physical pharmacy and pharmaceutical research at the Philadelphia College of Pharmacy and Science and associate in dermatology at the University of Pennsylvania's Graduate School of Medicine, has been appointed professor of pharmacy and chairman of the department at the Wayne State University College of Pharmacy.

Howard L. Hamilton, professor of zoology at Iowa State University, has been appointed chairman of the university's department of zoology and entomology.

Bernard N. Halpern, director of the Allergy and Immunology Research Center, Hôpital Broussais, Paris, has been appointed professor and head of the department of experimental medicine, Collège de France, Paris.

Merle Lawrence, professor of otolaryngology and physiology at the University of Michigan Medical School, has been named director of the university's new Kresge Hearing Research Institute.

Mahlon B. Hoagland, associate professor of bacteriology and immunology at Harvard, has been named the university's first Ruby Boyer Miller fellow in medical research.

Arthur P. Long, retired colonel and chief of the preventive medicine division of the Army Surgeon General's Office, has been appointed professor of environmental medicine and codirector of the International Center for Medical Research Training at the University of California.

Donald H. Loughridge, physicist and head of the physical research department at General Motors Research Laboratories, has been appointed director of applied research management with the Aerospace Corporation, El Segundo, Calif.

Jesse L. Bollman, emeritus consultant in medical research at the Mayo Clinic and director of research for the Rochester (Minn.) State Hospital, has received the Julius Friedenwald medal of the American Gastroenterological Association.

Ragnar Granit, director of the Nobel Institute for Neurophysiology, Stockholm, and visiting professor at the Rockefeller Institute, New York, has received the Anders Jahre prize of Oslo University and the third Saint Vincent prize for Medical Sciences awarded by the Academia di Medicina of Turin.

Olaf A. Hougen, professor of chemical engineering at the University of Wisconsin, has been appointed science attaché for the Scandinavian nations with the U.S. embassy in Stockholm, Sweden.

Hilton A. Smith, professor of chemistry at the University of Tennessee, has been appointed dean of the university's graduate school and coordinator of research.

Mariano Guiducci, organic chemist at the Squibb Institute for Medical Research, is the first winner of the institute's annual fellowship award. The $15,000 grant provides for leaves of absence of up to 39 months in order to allow staff members to obtain advanced degrees.

Larry Stein, research psychopharmacologist at Wyeth Laboratories' Basic Medical Sciences Research Division, has received the A. E. Bennett Neuropsychiatric Research Foundation award.

Roland H. Alden, chief of the University of Tennessee's division of anatomy, has been named dean of the university's School of Biological Sciences.

Preston Cloud, Jr., of the U.S. Geological Survey, has been appointed chairman of the department of geology at the University of Minnesota. He succeeds **George A. Thiel**, who is retiring.

Martin A. Elliott, director of the Institute of Gas Technology, has been appointed academic vice president of the Illinois Institute of Technology.

Philip N. Powers, head of Purdue University's department of nuclear engineering, has been appointed vice-president of the Purdue Research Foundation.

Luis Sequeira, on leave from his duties as scientific director of the United Fruit Company's Coto Research Station, Costa Rica, has been appointed associate professor of plant pathology at the University of Wisconsin College of Agriculture.

Recent Deaths

K. S. Krishnan, 63; physicist and director of India's National Physical Laboratory, a member of the Indian Atomic Energy Commission, and chairman of the Board of Nuclear Science; 13 June.

Francis F. Lucas, 76; metallographist and microscopist with Bell Telephone Laboratories from 1902 until his retirement in 1949; 20 June.

Ernest S. Reynolds, 76; research associate professor at the University of Miami's Institute of Marine Science; 31 May.

Thomas A. Stephenson; marine biologist and professor of zoology at the University of Wales since 1940; 3 Apr.

Frederick T. Thwaites, 77; emeritus professor of geology at the University of Wisconsin; 7 June.

Erratum: Seven lines were improperly placed in last week's news report on Project Chariot. The last two sentences of the first paragraph under the heading "CNI conclusions" (p. 2001) should have appeared at the end of the paragraph beginning "AEC officials . . ." in the preceding column. That paragraph would then read: "AEC officials complain that the [CNI] report is neither as accurate nor as complete as the general public might suppose. They point out, for example, that the CNI assertion that the strontium-90 yield might be 10 times greater than the AEC believed likely was based on a misreading of an AEC-sponsored study. This study gave 5 percent as the most probable portion of the total radioactive yield that might get into the fallout. But it also estimated that for the particular fallout constituent CNI was concerned with, strontium-90, the most probable figure would be 25 percent. Thus the figure could be underestimated, at most, by a factor of 4, not by the factor of 10 calculated by CNI."

Erratum: In the report "Simple method for measuring heart vector of isolated animal hearts [*Science* 133, 1831 (9 June 1961)], by C. V. Nelson, the data for the rabbit heart experiments are given incorrectly in the first sentence of the last paragraph on page 1831. This sentence should have read: "In four rabbit heart experiments in the larger sphere, the average peak vectors were 235 μa-cm for QRS and 100 μa-cm for T."

Reports

Harmonic Oscillation as Model for Cortical Excitability Changes with Attention in Cats

Abstract. A single shock to the prepyriform cortex with implanted electrodes caused a damped, sinusoidal oscillation in potential. The root-mean-square amplitudes of potentials evoked by short trains of stimuli, when plotted against the frequency of stimulation, fitted the equation for forced harmonic oscillation when the cat was attentive to the stimuli.

An attentive animal is necessarily awake and will respond to some events in its environment but not to others. The pattern of excitability for each animal is variable and can be modified systematically by learning. A relevant response to a particular stimulus does not necessarily imply attention, since there is always some level of probability that the response occurs accidentally in conjunction with the stimulus. By increasing the complexity of choice or the number of choices, this probability can be reduced to any selected level. In this case, attentiveness may be defined as a state of selective excitability to a patterned stimulus over a predetermined number of trials, without resort to anthropomorphic interpretation of what an animal is "thinking." On the other hand, failure of an animal to respond to a particular stimulus does not necessarily imply inattention, although concomitant responsiveness to other stimuli gives a strong possibility of this.

Recent work on the phenomenon of attention has centered on modification of cortical electrical activity by manipulations of behavior involving perception, often in conjunction with localized electrical stimulation of the diencephalon and brain stem. Basically, the same technique was used here in a form first employed by Nielson, Doty, and Rutledge (*1*). Cats were trained to perform a response upon receipt of an electrical stimulus to the cortex. Changes in the electrical potential evoked in the cortex by that stimulus were then correlated with changes in overt responsiveness.

Two or more pairs of electrodes were implanted in the prepyriform cortex of each of six cats, one pair for stimulation and the other for recording. Three of the cats were trained to proceed down a runway to reach food upon receipt of an electrical stimulus to this cortex. Training was in three stages: (i) An electrical stimulus was delivered at sufficiently high intensity to elicit an orienting response (sniffing, erection of the ears, turning of the head and eyes, and so forth), which occurred at stimulus intensities just below threshold for convulsions. (ii) Standard operant conditioning was carried out with the high-intensity electrical stimulus as the signal and milk as the reward. (iii) After establishment of the response, the stimulus intensity was reduced to a level 1.3 times that of the threshold for the behavioral response. In this circumstance the threshold intensities for both the electrical and behavioral responses were approximately the same. The other three cats were stimulated electrically in identical fashion but not in association with a reward.

The parameter of electrical change chosen for study was the graphic curve relating the root-mean-square amplitude of evoked potential to the frequency of electrical stimulation. Previous studies of the prepyriform-evoked potential (*2*) had shown that, when short bursts of electrical stimuli were delivered to the cortex at different frequencies, the maximum peak-to-peak transcortical amplitudes of response occurred at stimulus frequencies approximating the commonest frequencies of spontaneous cortical activity. The resemblance of this relationship to that inherent in harmonic oscillation, together with the sinusoidal nature of the spontaneous activity, suggested that the degree of peaking (Q) of the amplitude-frequency curve might change with fluctuations in attention. This was further substantiated by the facts that the potential evoked by a single shock delivered to the cortex strongly resembled damped sinusoidal oscillation; that the degree of apparent damping diminished when the cats became attentive to the stimulus and increased with habituation to the stimulus; and that both evoked and spontaneous wave forms were commonly seen at frequencies approximately one-half that of the dominant frequency, especially after training to respond to the stimulus.

In the present study (*3*) the root-mean-square amplitude of evoked potential was used in preference to peak-to-peak amplitude. The electronic techniques and the methods for determination of stimulus parameters will be described elsewhere (*4*). An important condition of measurement was

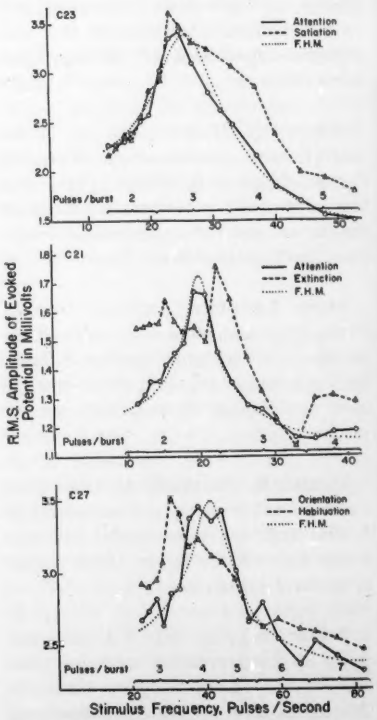

Fig. 1. Response amplitude-stimulus frequency curves from attentive and inattentive cats, compared with curves derived from the equation for forced harmonic motion (F.H.M.).

Instructions for preparing reports. Begin the report with an abstract of from 45 to 55 words. The abstract should *not* repeat phrases employed in the title. It should work with the title to give the reader a summary of the results presented in the report proper.

Type manuscripts double-spaced and submit one ribbon copy and one carbon copy.

Limit the report proper to the equivalent of 1200 words. This space includes that occupied by illustrative material as well as by the references and notes.

Limit illustrative material to *one* 2-column figure (that is, a figure whose width equals two columns of text) or to *one* 2-column table or to *two* 1-column illustrations, which may consist of two figures or two tables or one of each.

For further details see "Suggestions to contributors" [*Science* 125, 16 (1957)].

that the duration of recording of bursts of potentials was fixed, so that with changes in stimulus frequency the number of stimuli in each burst also was changed.

Three types of results are shown in Fig. 1. The points in C23 connected by the heavy line represent values of the amplitude of potentials evoked at each of a range of frequencies, in a cat which gave a response at each presentation of the electrical stimulus, there being no more than one false-positive response in each ten trials and no negative responses. The points connected by the broken line represent values obtained from the same cat and with the same stimulus parameters after free feeding, until the animal no longer responded to the electrical stimulus, but did so to other events in its environment, for example, the approach of another cat. The demonstrated change in the form of the curve did not take place immediately after satiation but rather after an additional half-hour of repeated negative trials.

The points in C21 connected by the heavy line represent values of amplitude from another cat in the same circumstances as in C23. The points connected by the broken line represent values obtained after extinction of the response by omitting the reward. Again, this change did not follow immediately upon cessation of response but after repeated negative trials.

The points in C27 connected with the solid line represent values from one of the control cats after elicitation of the orienting response with a strong electrical stimulus, the stimulus intensity thereafter having been reduced to 1.3 times threshold for the electrical response. The points connected by the broken line represent values obtained after 6 days of repeated electrical stimulation with habituation; that is, the cat was in the same environment as C23 and C21 but with no significance being attached to the stimulus.

The dotted curve in each of the three examples was derived from the equation describing forced harmonic motion in a system driven by a sinusoidal force:

$$m\frac{d^2x}{dt^2} + r\frac{dx}{dt} + kx = F\cos\omega t$$

As applied to an electronic oscillator, the constant m would represent inductance, r resistance, and k the reciprocal of capacitance. Although each of these elements has been described in squid axon (*5*), no physical meaning was assigned to them in the present study. The equation was used in one of its integrated forms:

$$E = \frac{F}{\omega\{r^2 + [(k/\omega) - \omega m]^2\}^{\frac{1}{2}}} + C$$

where E represents amplitude, F the driving force (dependent only in part on stimulus intensity), ω the stimulus frequency times 2π, and C an arbitrary constant of unknown significance. Use of the equation in this form implied two approximations: (i) that despite the shortness of the bursts (115 msec) the amplitude represented predominantly the steady state rather than the transient response; and (ii) that the driving force was sinusoidal, whereas in actuality it was impulsive. By these assumptions calculations were avoided, which were prohibitively complex for this preliminary stage of analysis.

These results show that the empirically derived relationship between the amplitude of evoked potential and the frequency of electrical stimulation corresponds to the analytical function describing forced harmonic motion, in states wherein the stimulus influences overt behavior at intensities well below convulsion levels. It may be inferred that when the cat is attentive to a stimulus, the cortex upon which it falls becomes (in a formal sense) resonant to that stimulus. In states of habituation, satiation, extinction, and also sleep, which alike imply the probability of inattention, the correspondence is not apparent. The change in form of the curves is compatible less with increased damping than with some disorganization of the cortex manifested by the appearance of two peaks of amplitude in the place of one.

The agreement between the observed and calculated data implies that the periodic activity of the cortex is harmonic, but it does not specify the mechanism, that is, whether the property of oscillation is inherent in the physicochemical structure of single neurons or in chains of neurons forming reverberating circuits. However, it does specify the need for further studies of the resistive and reactive properties of neurons and neuroglia, as well as comparison of the frequency-specificity of the excitability change with amplitude changes previously found to accompany changes in attention (*6*).

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13 February 1961

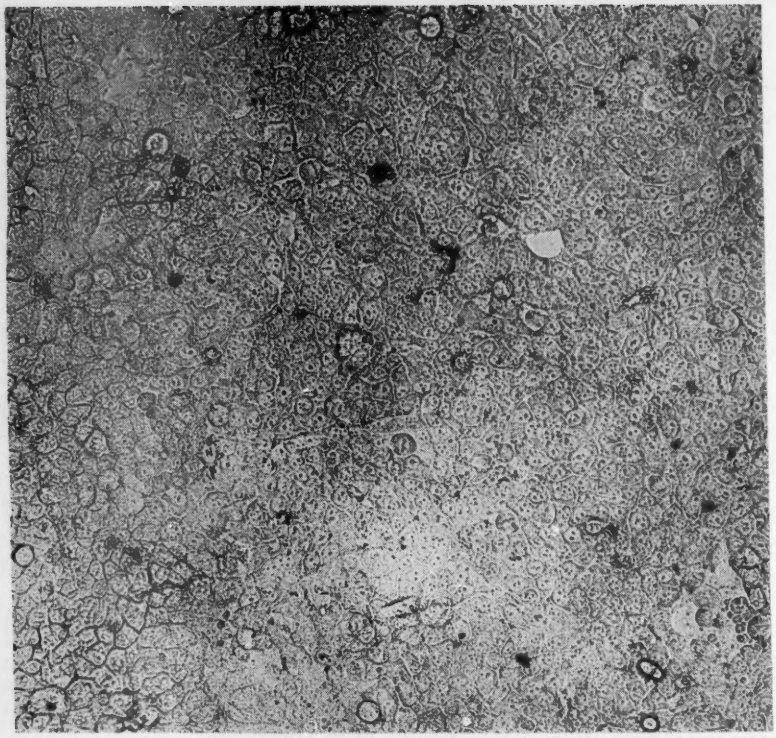
Isolation of Viruses from Children with Infectious Hepatitis

Abstract. Cytopathologic agents were isolated from 14 of 22 Indian children involved in an outbreak of infectious hepatitis in Arizona. Isolation was made in a serially transplantable cell line originating from human embryonic lung. Efforts to identify these agents as known viruses, by utilizing standard techniques, have been unsuccessful.

A serially transplantable cell line highly susceptible to viral infections was isolated from human embryonic lung during studies on the etiology of viral gastroenteritis. The superiority of these cells over established lines in primary isolation of enteroviruses (*1*) prompted attempts to isolate viruses from the feces of patients with clinical symptoms of infectious hepatitis.

In October 1959 an epidemic of infectious hepatitis was observed on an Indian reservation in eastern Arizona. There were 22 hospitalized cases of this disease in children varying in age between 20 mo and 3 yr. The course of the disease was severe, and protracted hospitalization was required in a majority of the cases. Scleral icterus was noted in all cases, although dermal icterus was not pronounced because of dark pigmentation. All urines were strongly positive for bile pigments, serum icterus indexes were elevated, and stools usually were clay colored. The clinical diagnosis of all 22 children was infectious hepatitis.

Tissue cultures were prepared as outlined previously (*1*) and changed to a maintenance medium of 2 percent calf serum and M199 prior to inoculation of the fecal specimens. Twenty percent fecal suspensions were prepared for inoculation into tissue culture according to methods described by Paul (*2*). One-tenth of a milliliter of 20 percent fecal suspension and 0.9 ml of maintenance medium were



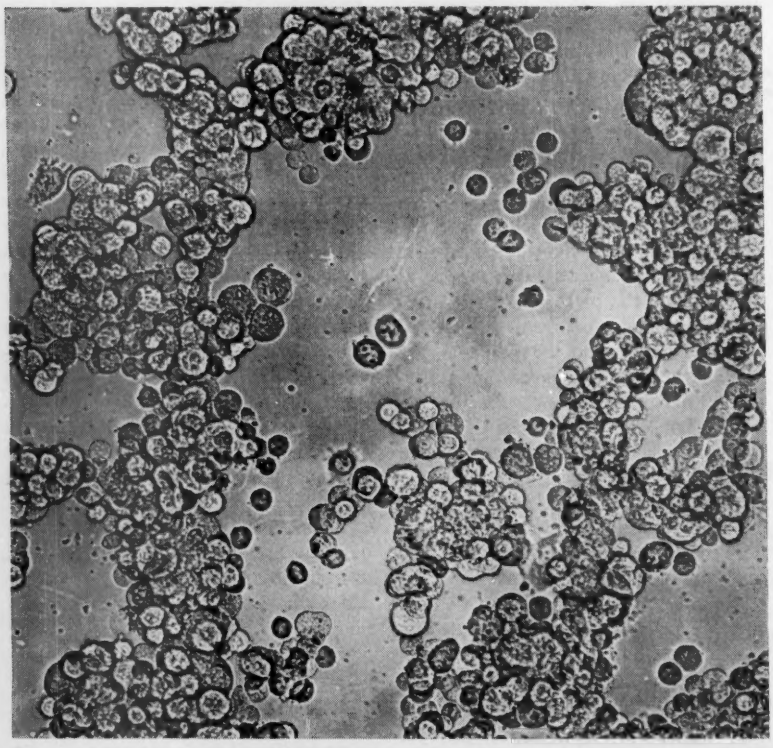


Fig. 1. (Top) Living culture of embryonic human lung cells. (Bottom) Same culture, 72 hr after infection, showing typical cytopathology of the Arizona viruses isolated.

added to each culture tube. Incubation was carried out at 37°C in a standard roller-tube apparatus.

First passages were characterized by marked phagocytosis of colloidal fecal particles producing a generalized cytoplasmic granularity. Viral cytopathogenicity, however, was indicated on the 5th day after infection by rounding, ballooning, and eventual clumping of infected cells. The clumping observed was strikingly characteristic of an agglutination-type reaction. Subsequent passages eliminated granularity and showed a consistent viral cytopathic effect (see Fig. 1).

Serially transplantable cytopathologic agents were isolated from 14 of the 22 children examined. Only one isolation was made from 23 persons without apparent symptoms of infectious hepatitis. These latter persons, ranging in age from 1½ mo to 66 yr, were familial contacts of the acute cases. The single isolate was from a 2-yr-old sibling of an acute case. Specimens taken from one of two children with clinical diagnosis of diarrhea in the same hospital yielded a virus indistinguishable from those isolated in the overt hepatitis cases.

With a single exception, attempts to isolate these viruses in primary renal epithelial culture of *Macacus rhesus* were unsuccessful after three serial passages.

Antisera against known enteroviruses (*3*)—Echoviruses 1-28, Coxsackie B viruses 1-6, Coxsackie virus A-9, and three poliovirus types—failed to neutralize against 10, 100, 1000 $TCID_{50}$ of each isolate.

Suckling mice remained well when inoculated intracerebrally, intramuscularly, or intraperitoneally; similarly, the viruses introduced into the allantoic or amniotic cavities of 7-day embryonated eggs were without effect. No demonstrable infection was observed when the isolates were placed on the scarified cornea of adult albino rabbits. Complement fixation, with adenovirus antiserum, was undetectable at serum dilutions of ¼ and ⅛. Hemadsorption or hemagglutination could not be detected when using guinea pig, human cells from blood types A, B, and O, or adult or 1-day-old chicken erythrocytes. Hemagglutination of *Macacus rhesus* erythrocytes occurred sporadically and appeared to depend on the animal from which the cells were

obtained. The growth pattern of the viruses is unlike that of cytomegaloviruses (*4*).

The agents survive a temperature of 60°C for 40 min. Infectivity titers for embryonic human lung cultures vary from $10^{-3.5}$ to $10^{-5.5}$. Cross protection tests with convalescent sera indicated a serologic relationship between 13 of the 14 isolates. The only exception was the virus which grew in the monkey renal cultures. Acute sera from four of the hospitalized patients failed to neutralize homologous viral isolates, whereas sera from 1-yr convalescents neutralized 100 to 1000 $TCID_{50}$ of virus at serum dilutions of 1/25 and 1/50. Sera obtained from two adults who had recovered from infectious hepatitis 1 yr previously neutralized all the viruses except the monkey kidney isolate. The neutralization index with the latter sera was as great as that of convalescent sera from hospitalized cases (*5*).

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13 March 1961

Gibberellin as Sex Regulator in Ricinus communis

Abstract. Spraying monoecious inbreds with gibberellin A_3 can markedly increase their female tendency. The effect of this substance upon sex appears to simulate the action of long days.

The castor bean, *Ricinus communis* L., is a monoecious, potentially everflowering perennial. The main stem, which blooms first, and all subsequent shoots, are terminated by racemes, and each raceme differentiates both staminate and pistillate flowers. The percentage of pistillate flowers in the racemes of individual plants is taken as a measure of their female tendency. This character is subject to extreme genetic and nongenetic variations.

Table 1. Effect of spraying seedlings with gibberellin upon the female tendency of a monoecious inbred of the castor bean. Figures in parentheses refer to the total number of flowers. The spraying regimes are given in the text.

Treatment	Individual plants employed	Pistillate flowers (%) in sequential racemes			
		First	Second	Third	Fourth
		Sprayed			
A	108-1	86.5(37)	100.0(41)	92.7(55)	34.7(101)
A	108-2	87.9(83)	100.0(85)	73.9(85)	73.9(130)
B	108-3	66.0(97)	97.6(42)	44.7(132)	40.8(49)
B	108-4	74.6(63)	88.7(53)	59.4(69)	36.3(113)
C	108-5	57.9(107)	73.8(84)	38.6(132)	21.1(109)
C	108-6	61.2(67)	93.5(46)	38.0(108)	26.2(130)
		Unsprayed			
	108-7	27.4(72)	15.8(101)	12.9(109)	29.4(167)
	108-8	32.8(67)	24.2(62)	14.7(75)	14.9(134)
	108-9	31.7(83)	19.7(71)	18.4(76)	25.6(78)
	108-10	25.7(105)	24.3(66)	15.8(54)	25.8(159)
	108-11	32.1(84)	18.2(88)	13.2(91)	27.1(151)
	108-12	27.3(77)	25.9(81)	17.4(115)	24.5(188)

In connection with a study of the relationship between female tendency and the incidence of female mutants in monoecious inbreds (*1*, *2*), a search was made for substances which might regulate sex expression in these inbreds.

Previous investigations demonstrated that in monoecious inbreds of cucumbers, *Cucumis sativus* L., certain treatments with 1-naphthalene acetic acid (NAA) increase (*3*) and certain treatments with gibberellic acid or gibberellin (GA) decrease (*4*) female tendency. It is also known that staminate flowers can be induced by GA in some genetic females of cucumbers (*5*, *6*). These findings prompted us to test NAA and GA as possible sex regulators in the castor bean.

Various spraying regimes with NAA at concentrations ranging from 10 to 100 parts per million (ppm) did not affect female tendency. On the other hand, spraying with GA markedly increased female tendency (Table 1). In the experiment with GA, I used an early-flowering monoecious inbred No. 108 which was self-reproduced for 11 generations. This inbred was originated from a selection made in the variety Gamadon (*1*). The seed was germinated at 30°C on 8 August 1960, and 12 uniform plants were grown in 12-in. pots, in soil, under greenhouse conditions, without supplementary light, at day temperatures of 24° to 27°C and night temperatures of 18° to 21°C (thermostatically controlled). The sprayed and unsprayed plants were randomized.

The sprays used were aqueous solutions of Merck's Gibrel, a potassium salt of gibberellin A_3. Each treated plant was sprayed three times—at the two-leaf, three-leaf, and four-leaf stages of growth, successively. In treatment A, the concentrations of the gibberellin solutions employed were 1500 ppm for the first spraying, 1500 ppm for the second, and 500 ppm for the third. In treatment B, the corresponding concentrations were 1500, 1000, and 500 ppm; and in treatment C, they were 1500, 500, and 125 ppm (Table 1). The spraying began on 26 August and the first racemes appeared on 8 September. In both sprayed and unsprayed plants the number of leaves to the first raceme on the main stem ranged from six to eight and averaged seven.

By selective pruning of side shoots it was possible to obtain four sequential racemes on each plant, and these racemes were developmentally comparable in all plants.

As is shown in Table 1, the first three sequential racemes on each of the six sprayed plants were greatly affected by the GA treatments. One should also note the trend in the differences between treatments A, B, and C.

In the unsprayed plants (Table 1) there is a drop in female tendency from the first to the third raceme in each individual, and this drop is followed by a recovery in the fourth raceme. The racemes of the sprayed plants do not exhibit the same developmental change, presumably because of the cumulative effect of the three GA treatments at seedling stages. Cyclic changes in sex tendency during development are not uncommon in some untreated monoecious species of plants (*6*).

It is evident that GA is an effective substance for increasing female tendency in the castor bean. Other GA experiments with inbred No. 108, as well as with several distinctly different mono-

ecious inbreds, support this conclusion. The effective range of concentrations is between 250 and 1500 ppm of potassium gibberellate, but the particular spraying regime to be used would depend on the objective of the experiment and the variety employed.

The increase in female tendency after GA treatments is often associated with: (i) increase in internode elongation, (ii) decrease in leaf size, (iii) suppression of shoot development at some lateral leaf axils, and (iv) delay in flowering.

It is essential to emphasize the importance of time in plant development at which the GA treatment is applied. If the application of GA is limited to a period prior to the differentiation of the first flower primordia, a prolonged delay in flowering will occur, and, during a long delay, the effect of GA upon sex is nullified. If this aspect of timing is overlooked, one may arrive at an erroneous conclusion concerning GA as a sex regulator, particularly in treating late-maturing varieties.

The most significant fact emerging from these results, in light of other reports, is that GA treatments of cucumber and castor bean plants provoke diametrically opposite changes in sex expression. Perhaps it is not a mere coincidence that the two species exhibit also opposite sex responses to photoperiod variation. In cucumbers, short days increase and long days decrease female tendency (*7*). In castor beans, the reverse seems to be true (*1*). Thus, in the two species involved, the effect of GA upon sex appears to simulate the action of long days (*2*).

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16 February 1961

Identity of a Fungus Causing Blue Stain in Balsam Fir

Abstract. Blue-stained balsam fir wood [*Abies balsamea* (L.) Mill.] consistently yielded cultures of a nonsporulating fungus which were found to be the same as those obtained from ascospores of *Amphisphaeria thujina* (Peck) Sacc. collected from dead branches of this host. This blue stain appears to be identical with a previously reported but hitherto unidentified stain of conifers. The association of *Amphisphaeria* with stain in living trees does not appear to have been recognized before.

During the past 25 yr several investigators have reported the occurrence of a blue stain in the heartwood of balsam fir, but were unable to identify the causal organism. Kaufert (*1*), in 1935, described a blue stain occurring in the heartwood of overmature balsam fir in the Lake states. The fungus isolated from this stain produced "luxuriant grey-blue" mycelium in culture, but was not identified. A few years later, Crowell (*2*) described a blue stain of heartwood of white spruce and balsam fir from Shelter Bay, Quebec. He reported that the "bluestain was unusual in that almost the entire heartwood was deeply stained while the sapwood was free from attack," adding that "stained wood showed many short blackish lines on the radial surface, but the lines were not necessarily associated with wood rays, as invariably occurs in other stained wood." When blocks of wood were kept in a moist chamber for 5 wk, dark, olivaceous, cottony hyphae grew out of the stained wood but formed no spores. Interest in the blue-staining fungus was revived in 1942 when Christensen and Kaufert (*3*) confirmed that the fungus mentioned earlier by Kaufert was the same as that described by Crowell. They consistently isolated the same fungus from a blue stain of heartwood of northern white cedar (*Thuja occidentalis* L.) in Minnesota. Numerous isolations had yielded, in almost every case, a nonsporulating and very slow-growing fungus with dark hyphae, which was concluded to be the organism chiefly or solely responsible for the stain in the wood.

Although the presence of blue stain with heart rot in conifers has been recognized in Quebec for several years, only recently has its prevalence in branch stubs of balsam fir been observed. Blue stain was observed in over half of 648 living and dead branches that were sampled at Duchesnay, Quebec, in 1960, and a characteristic fungus was consistently isolated from the stained wood. The stain occurred as streaks at the bases of the branches, frequently extending for distances of 1 to 2 in. into the buried portion of the branch. There was no evidence that the discoloration had spread from the branches into the surrounding healthy wood, although the stain fungus was isolated several times from what appeared to be normal heartwood, as well as from areas of typical blue-stained wood adjacent to heart rot. Blue stain was not observed in branches which had been dead for less than 10 yr. The characteristics of the stained wood agreed both macroscopically and microscopically with the descriptions and illustrations of blue stain that have appeared in the earlier reports. The infected wood, both in radial and tangential sections, displayed numerous dark lines running at right angles to the wood elements, often continuing the characteristic pattern through adjacent areas of decayed wood. Sections of stained wood examined microscopically revealed long strands of thick, dark hyphae which were constricted where they passed through the walls of tracheids and rays.

On malt agar slants, the fungus produces abundant, sterile, dark grey-olivaceous aerial mycelium. The colonies have abrupt clear-cut margins, the reverse of the culture being black. At room temperature the growth is slow; it covers about two-thirds of the slant in 3 wk and usually ceases entirely before reaching the end of the tube.

The isolates from the blue stain were identified by comparing them with cultures made from fruiting structures found on dead branches of balsam fir. Dead branches, in various stages of deterioration, from stands where the blue stain occurred were critically examined for fruiting-bodies of fungi. From one of these fungi, seven cultures (representing three separate collections) were obtained that appeared to be identical with the cultures from the stained wood. This fungus was recognized as belonging to the genus *Amphisphaeria*.

In the literature, a number of species of *Amphisphaeria* are described which appear to be similar to the fungus collected on fir at Duchesnay, but the description of *A. thujina* (Peck) Sacc. agrees most closely in respect to the size of the perithecia and of the ascospores. The original collection of *A.*

thujina was made from dead branches of *Thuja occidentalis* in New York about 1875, and was deposited in the New York State Museum. Positive identification of this ascomycete was made by comparing the type collection (*4*) with the Duchesnay material.

To test the ability of the fungus to produce blue stain, blocks of balsam fir were inoculated with cultures of *Amphisphaeria thujina* derived both from stained wood and single ascospores. After 2 mo, typical blue stain had developed in all of the test blocks. The fungus was reisolated from the artificially inoculated wood and identified as the species first isolated. These experiments prove that *A. thujina* is the causal agent of the blue stain in balsam fir (*5*).

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4. We are grateful to S. J. Smith, curator, New York State Museum, for his kindness in providing the type collection of *A. thujina*. A detailed description of *A. thujina*, including the results of comparative taxonomic studies with Peck's original material, is in preparation.
5. Further laboratory studies are in progress to determine the factors that may influence the establishment of blue stain in the living tree, and to ascertain its effect on subsequent development of decay organisms. This report is contribution No. 723, Forest Entomology and Pathology Branch, Department of Forestry, Ottawa, Canada.

30 January 1961

Freezing-Out, a Safe Technique for Concentration of Dilute Solutions

Abstract. The principle of freezing-out has been adapted for the quantitative concentration of small or large volumes of dilute solutions. Mechanical stirring is an essential part of the process. The method should prove of greatest value where volatile or heat-labile substances are to be concentrated and is applicable to solutions in certain organic solvents as well as to aqueous solutions.

The purpose of this report is to call attention to an exceedingly useful, but hitherto neglected, method for the laboratory concentration of dilute solutions. The method, which possesses advantages over most of those in use, is based on the principle of freezing-out. It is simple, relatively inexpensive, and is almost above reproach with regard to chemical or physical alteration of the substances being concentrated. The method is applicable to a very wide range of volumes, having been used in this laboratory on samples as small as 100 ml and as large as 300 liters. Preliminary work has shown that in addition to its use with aqueous solutions it is applicable also to solutions in organic solvents, such as benzene, which solidify at relatively high temperatures.

Although freezing-out is widely used industrially, it has not become a part of the analyst's armamentarium, and references to its use in the laboratory are rare. As described below, the method is similar to that used in the purification of benzoic acid by Schwab and Wichers (*1*). It differs from the previous applications by Haurowitz (*2*), Gibor (*3*), and Schildknecht and Mannl (*4*), in that mixing is an essential part of the process and part of the solution is left unfrozen. Thus materials which are adversely affected by freezing are not harmed, and substances which dissolve with difficulty are recovered while still in solution. In addition, the volumes which can be concentrated are much greater than in the previous applications.

Volumes of 1 liter or less are treated as follows. The solution is poured into either a glass or plastic bottle, leaving sufficient room for the expansion which accompanies freezing. The bottle is then attached to a mechanical shaker and placed in a freezing chamber. After several hours of gentle shaking, most of the solution will be frozen except for the central spherical or egg-shaped portion which contains the concentrated solutes. This portion is recovered by punching or melting a hole in the ice and pouring it out. The equipment used in this laboratory consists of a freezer cabinet of the type used to store ice cream, operating with a ⅓-hp motor at −30°C, and a Burrell Wrist Action shaker which rests on the wooden cover of the freezer. Arms with clamps attached extend down into the freezer from the shaker. In this way numerous samples of different volumes can be concentrated simultaneously. The results with this method have been excellent, with recoveries of greater than 99 percent after concentrations of as much as 20-fold in volume. However, in order to achieve such recoveries, it is essential to keep a close watch over the bottles so that they may be emptied when cloudy ice indicates that entrapment is occurring.

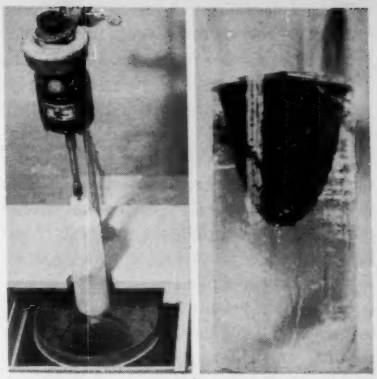

Fig. 1. (Left) A 5-gal container in the freezer chest with the polyethylene bottles on the stirrer. (Right) The block of ice removed from the container showing the concentrate in the core.

Large volumes are treated somewhat differently. The solutions are placed in cylindrical metal containers which are positioned in the freezing chest so that the open tops of the containers are just above the freezing level in the chest (Fig. 1). The solutions are stirred mechanically, and the propeller is raised in several steps as freezing proceeds. Ice forms from the sides inwards and from the bottom upwards, and the result is a smooth, sharply defined shallow conical core in which the solutes are concentrated into a small volume (Fig. 1).

The time required for concentration varies with the volume and the efficiency of operation. For example, with the equipment in use it has been possible to concentrate three 16-liter containers of water to a volume of 1 liter each in about 50 hr. On the other hand, when the solution was placed directly in the compartments of the cabinet instead of in containers, 300 liters were concentrated to 35 liters in the same length of time.

Several refinements are possible. To avoid losses due to splashing of the concentrate onto the top of the already formed ice, two 250-ml polyethylene bottles, bored through the cap and bottom, are slipped onto the stirring shaft (Fig. 1). Thus, as the stirrer is raised the liquid level falls. Recovery of the last traces of concentrate from the core is simplified by gently melting the surface ice with warm air, such as from

a hair dryer. Contact of the solutions with the metal of the containers may be avoided by lining the containers with polyethylene bags. This does not affect the freezing rate, provided that the spaces between the bag and container wall are filled with water. The containers must be nearly filled to begin with, but the necessity of having many different sized containers available can be eliminated by using a core frozen to the proper capacity.

Occasionally entrapment will result in losses, and the easiest way to recover the lost material is to thaw the sample and freeze it again. However, any losses which do occur are nonspecific and do not result in fractionation. Thus any easily measured parameter such as conductivity or optical absorbance will serve to indicate the recovery of the whole. Another phenomenon which sometimes occurs is supercooling followed by the formation of ice throughout the solution. It has been found that this rectifies itself and does not interfere with the final result.

Since the success of the procedure, or at least its application to a larger scale than that of Haurowitz, or Gibor, or Schildknecht and Mannl, depends upon stirring, it is worth-while describing what seems to be a plausible hypothesis for its necessity. In a quiescent solution, as ice is formed, the salts eliminated from it dissolve in the adjacent layer of solution and lower the freezing point of this layer. Thus the temperature of the layer is allowed to fall below the freezing point of the rest of the solution. Then, that part of the solution immediately adjacent to the layer, not having the higher salt content of the layer, becomes supercooled and may suddenly freeze, trapping the layer with its content of salts against the ice, where it too subsequently freezes. Thus the purpose of the stirring is to prevent the formation of such layers. This hypothesis of Himes *et al.* (*5*) is supported by the appearance of ice formed during periods when stirring was interrupted. In these experiments such ice differed from the usual clear structureless ice in being laminated in appearance. The laminations, which were several millimeters in thickness, were blue as a result of entrapment of methyl violet which had been added to the solutions (*6*).

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6. In the hope that ready availability of the necessary equipment will encourage use of the methods described, arrangements have been made with the Virtis Company, Inc., Gardiner, N.Y., to manufacture and market such equipment. Part of the work was done during the tenure of U.S. Public Health Service research grant No. RG 7229.

20 February 1961

Fractionation of Tracer Effluxes during Action Potential

Abstract. The fluid flowing by the *Nitella* internode or squid giant axon loaded with radioactive cations was fractionated during the action potential. In this manner it was possible to ascertain the time course of efflux of these cation tracers during activity.

In the investigation with radioisotopes of transport phenomena in biological membranes, it is desirable to correlate the movement of radioisotopes with other rapid processes in the membrane, such as changes in electric potential and membrane conductance. It is known that the process of action potential production in the squid giant axon and in other excitable cells is associated with enhancement of loss of various univalent cationic radio-tracers to the extracellular fluid (for example, *1*). It was difficult, however, to decide with certainty in what phase of bioelectric activity this enhancement occurred. Wilde and co-workers (for example, *2*) have had some success in this direction. By perfusion of the coronary vessel of the whole heart, they were able to obtain a detectable efflux of potassium-42. There are, however, obvious ambiguities in their experiment as to the temporal relationship between the efflux and the electric response of the heart because of the impossibility of ascertaining the time required for diffusion of the isotope. In the present study, it has been possible to fractionate the radioisotope efflux during the action potential in single cells (*Nitella* and squid giant axon).

The principle of the method consists in running the fluid medium past the cell under study at a high speed and then fractionating it. A single cell of *Nitella* or a squid giant axon (both approximately 0.6 mm in diameter and 40 mm long) was introduced into a small chamber (1.2 to 2 mm in diameter) made of Lucite. The cell was kept approximately at the center of the chamber. The wall of the chamber was coated with melted paraffin. There were two pairs of platinum electrodes making contact with the fluid in the cavity. The upper opening of the chamber was connected to a large reservoir of fluid and, by virtue of the difference in the hydrostatic pressure, the fluid in the cavity was pushed through at the rate of about 50 to 150 cm/sec in the case of the *Nitella* cell and about 200 cm/sec in the case of the squid axon.

Fractionation of the running fluid was effected by a rotating Lucite disk (about 70 cm in diameter) provided with 40 to 200 small compartments near its edge. The disk was driven by a motor at about 1 rev in 30 to 60 sec in the case of *Nitella* and at the rate of approximately 1 rev/sec in the case of the squid axon. A source of light attached to the rotating disk and a stationary photocell were used to trigger stimuli (as well as the oscillograph used to record the action potential) at a given position of the disk. The Lucite chamber carrying the cell was held by a movable stand so that it could be quickly brought to, or moved away from, the rotating disk.

The middle diagram in Fig. 1 shows an example of the results obtained with a *Nitella* cell loaded with potassium-42. Electric stimuli were repeated at intervals of 2 min for a total period of 80 min. The running fluid (artificial sea water diluted by 500 with distilled water) was fractionated into portions containing effluxes obtained in 0.75-sec intervals. The samples of fluid in individual compartments of the rotating disk thus contained the radioactive potassium released during 40 successive cycles of activity. These samples were dried and measured by a standard radiation counter.

It is seen in the diagram that there is a small efflux of tagged potassium before stimulation and that this level of efflux was markedly enhanced after the delivery of a brief electric shock to the cell. The action potential recorded by this arrangement is "diphasic." With this action potential regarded as composed of two monophasic action potentials (with one of them reversed in phase and delayed by the interelectrode conduction time), the approximate time course of the potential variation under the upper recording

electrode was reconstructed and shown by the thin continuous line.

In all six experiments on *Nitella megacarpa* and five experiments on different species of *Nitella* (probably *flexilis*), it was found that the peak of the action potential roughly coincides with the peak of the efflux of tagged potassium. The slight discrepancy between the peaks of the two curves can be attributed partly to the difference in the time at which different parts of the cell reach the peak of activity. The retention of the radioactive potassium in some part of the path of running fluid is another factor that is responsible for the discrepancy in the peaks and also for the efflux after the end of the action potential. In a number of more recent experiments, it was possible to obtain a closer parallelism.

In this connection it is to be pointed out that Osterhout (*3*) had predicted an outward movement of K^+ during activity in *Nitella*. The time course of the efflux observed can be interpreted as a reflection of the increased membrane conductance during activity (*4*). Results from using cesium-134 and rubidium-86 instead of potassium-42 were qualitatively the same.

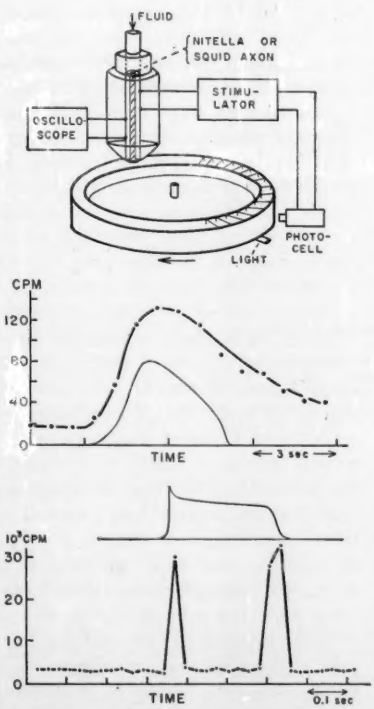

Fig. 1. (Top) Principle of the method of fractionating tracer effluxes during action potential (not to scale). (Middle) Efflux of K^{42} from a cell of *Nitella* (dots) during the action potential (thin continuous curve). (Bottom) Efflux of K^{42} from a squid giant axon treated with tetraethylammonium chloride (dots) during the action potential (thin continuous curve).

Using chloride-36 instead of tagged cations, we tried to demonstrate an increased efflux of tagged univalent anions during activity. We could bring the radioactivity of the cell up to 1000 count/min or slightly more. We could not influence the loss of this radioactivity from the cell by stimulation. We found also that complete substitution of the chloride ion in the medium with glutamate did not bring about any appreciable change in the amplitude of the action potential.

We encountered serious difficulties when attempts were made to apply the same technique to the squid giant axon which requires much higher time resolution in order to correlate the effluxes of tagged ions with the action potential. Such difficulties were partly overcome by prolonging the action potential by injecting tetraethylammonium chloride uniformly over the entire length of the axon. By this procedure, combined with a lowering of the temperature to about 7°C, it was possible to increase the duration of the action potential to 0.5 to 1.0 sec or more. We tried to reduce the thickness of the stagnant layer of the fluid by inducing turbulance in the running fluid around the axon. In several favorable cases, we could attain a time resolution up to the order of 20 msec. In many instances, however, the resolution was poorer than about 100 msec, and, as a consequence, we could not detect an increase in the efflux associated with the action potential. We attribute this variability in the time resolution to the variability in the thickness of the connective tissue layer on the surface of the axon.

The bottom diagram in Fig. 1 shows the result of one of six successful experiments in which the efflux of potassium-42 or sodium-24, or both, was investigated in axons treated with tetraethylammonium chloride. In this example, an isotonic potassium chloride solution containing potassium-42 was injected in a portion of an axon treated uniformly with tetraethylammonium chloride. It is shown in this diagram that there is one phase of increased efflux at the onset and another phase at the end of the prolonged action potential. There was no appreciable increase in the efflux during the plateau. A similar result, with double peaks in the efflux, was obtained with sodium-24. The ratio of the flux at the onset to that at the end varied considerably from preparation to preparation. At this preliminary stage of the experiments, it is not possible to make a definite statement as to this ratio. The results obtained on the relative impermeability of *Nitella* to chlorine-36 are contradictory to the experiments of Gaffey and Mullins on *Chara* (*5–7*).

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6. A report of our interpretation of the experiments presented here and their implications for prevailing concepts of excitation is in preparation. Recently it has come to our attention that C. Terzuolo is in the process of studying the efflux of isotopes from *Nitella* autoradiographically.
7. We are grateful to Mrs. W. J. V. Osterhout for her interest and help.

23 February 1961

Osteogenic Induction across Millipore Filters in vivo

Abstract. Immunization of host mice to homograft tissues prior to subcutaneous implantation of homograft bone within diffusion chambers did not prevent new bone formation on the host side of the filter, thereby indicating its origin from host cells in response to a diffusible osteogenic inductor from within the chamber rather than from undetected escaping homograft cells.

In a previous study (*1*) designed to provide information about the origin of newly formed bone around bone autografts, it was found that subcutaneous implantations of 2- to 3-day-old isologous mouse calvaria within Millipore diffusion chambers (*2*) for periods ranging from 2 to 8 wk resulted in the formation of new bone and cartilage exclusively *within* the chambers. In more recent experiments, bone formation on the host side of the filter (which

has a pore size of 0.45 μ) was obtained as well, if thinner (100 μ) Microweb filters were utilized or if homologous bone was implanted within chambers made up with "standard" thickness (150 μ) Millipore Microweb filters. However, the escape of isologous or homologous bone-forming cells from within the chamber could conceivably have accounted for these results, particularly since it was found that similar bone homografts implanted subcutaneously without the protection of a diffusion chamber showed excellent new bone formation after 2-wk implantation before any host reaction could develop. The following experiment, designed to distinguish by immunological means the source of new bone on the host side of the filter by bringing about early destruction of "escaping" homograft bone cells (should they escape at all), was performed.

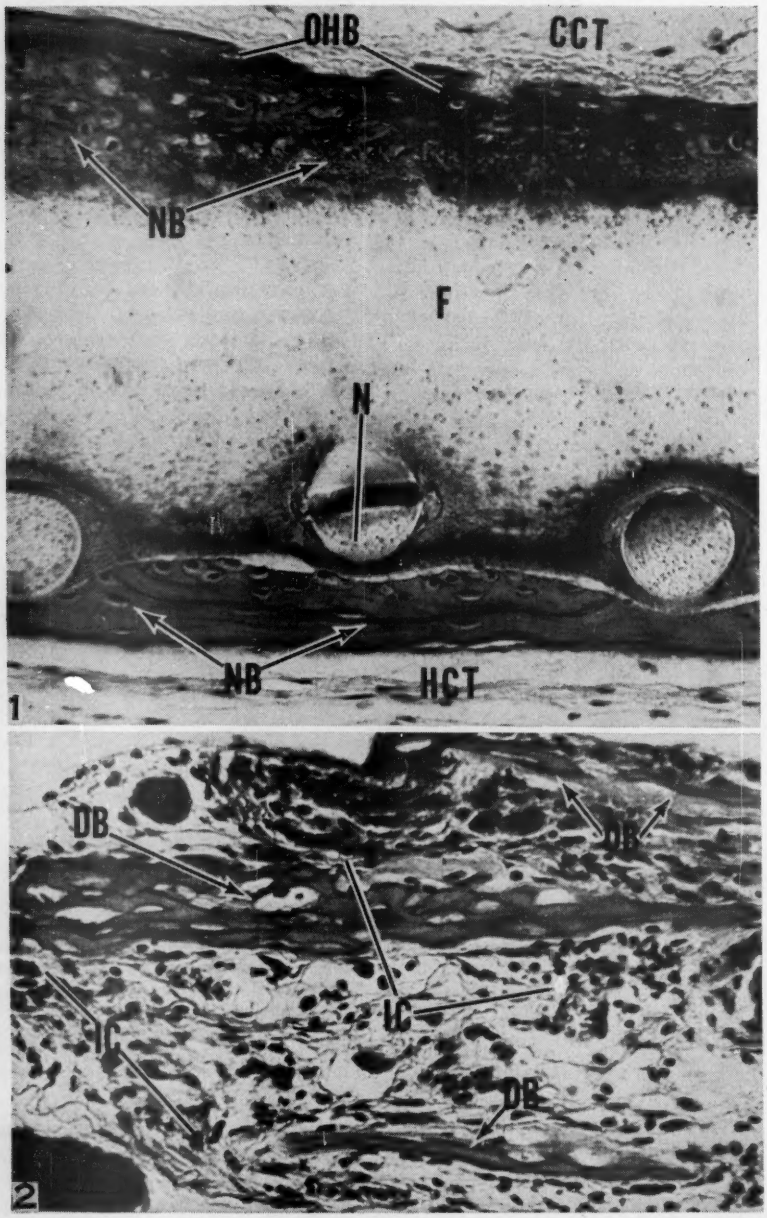

Fig. 1. Histological section (hematoxylin and eosin) of 2-mo chamber containing homograft bone in immunized host (× 185) shows new, vital bone with "resting lines" on host side of filter opposite less organized new bone on inner aspect of filter. Note dark staining "acellular zone" and basophilic droplets within body of filter. *OHB*, original homograft bone; *NB*, new bone; *F*, filter; *N*, cross section of nylon reinforcement; *HCT*, host connective tissue; *CCT*, chamber connective tissue. Fig. 2. Histological section (hematoxylin and eosin) of 2-mo free implant of homograft bone in immunized host (× 185) shows dead, fragmented bone surrounded by inflammatory cells. *DB*, dead bone; *IC*, inflammatory cells.

Young male Swiss albino mice (Webster strain) were immunized to tissues of C57 bl/6 mice by a modification of the technique of Algire *et al.* (*3*); three separate subcutaneous implantations, at 2-wk intervals, of spleen fragments from adults of the latter strain were used. After this 6-wk immunization period, a diffusion chamber containing half of a 1- to 2-day-old C57 bl/6 calvarium was implanted subcutaneously into each host, while the opposite half of the calvarium was implanted at some distance from the chamber as a "free implant" control. A duplicate, nonimmunized group was set up as well. Animals from both groups were killed at intervals of 2, 3, and 4 mo. Twenty-six intact chambers were recovered from immunized and nonimmunized animals. It was found that of 14 chambers recovered from *immunized* mice, slight to considerable patches of new, vital bone were noted on the host side of the filter in 12 animals. Characteristically, this new bone appeared opposite an area of new bone formation on the inner aspect of the filter (Fig. 1). On the other hand, the *free implant bone* in the immunized animals was uniformly found to be dead, surrounded by an inflammatory reaction, and it showed little, if any, attempt at new bone formation (Fig. 2). In the *nonimmunized* group, 9 of 12 intact chambers showed similar patches of new, vital bone on the host side of the filter. Although the free implant control bone showed in these nonimmunized animals evidence of extensive new bone proliferation at an earlier stage after implantation, the tissue appeared to be dead or dying and it was surrounded by inflammatory cells at the time that the animals were killed.

In view of the inhibition of new bone formation and the enhanced destruction of freely implanted bone homografts by the preimplantation immunization procedure, it is assumed that any homograft bone cells escaping from diffusion chambers in immunized animals would have suffered a similar

fate. It is therefore concluded that the new bone on the host side of the filter must have come from the host. With regard to the possibility that the Millipore filters per se were responsible for the bone induction, this seems unlikely in view of my inability in other experiments to demonstrate bone formation around freely implanted Millipore filter material as well as in view of the failure of other investigators (*4*) to note new bone formation on the host side of Millipore filters. Rather, the experimental results indicate that the new, vital bone found in immunized mice on the host side of diffusion chambers containing homograft bone is derived from host tissue in response to a *diffusible osteogenic inductor* coming from the new bone laid down on the inner aspect of the filter, thereby representing the in vivo extension of the in vitro findings of Grobstein (*5*) and Lash *et al.* (*6*) with respect to the passage of inductor substances through Millipore filters (*7*).

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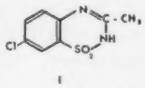
7. Further experiments are now in progress to determine the specificity and chemical nature of the diffusible osteogenic inductor reported here. This study was supported by the U.S. Army, Office of the Surgeon General, under contract No. MD-2018. I gratefully acknowledge the technical assistance of Miss G. Cirulis and G. Pettengill.

20 February 1961

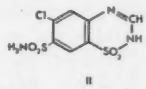
New Class of Antihypertensive Agents

Abstract. Effective antihypertensive agents of the benzothiadiazine series, devoid of diuretic activity, are described. There follows a method of synthesis and a description of the pharmacological activity of one of these substances.

We have synthesized 7-chloro-3-methyl-1,2,4-benzothiadiazine-1,1-dioxide (I), the first compound in the 1,2,4-benzothiadiazine-1,1-dioxide series in which a separation of the antihypertensive and diuretic activities has been achieved. A characteristic of the diuretic agent chlorothiazide (*1*) (II) and other related benzothiadiazine diuretics, including the 3,4-dihydro derivatives, is their property of moderately reducing the blood pressure of hypertensive subjects.



I



II

Although the precise mechanism of this action is not known, it has generally been assumed to be related to the diuretic and natriuretic properties of the compounds (*2*).

Compound I was synthesized as follows: 2,4-dichloronitrobenzene was converted into 2-benzylthio-4-chloronitrobenzene, with a melting point of 132° to 134°C (found: N, 5.03) by reaction with benzylmercaptan in the presence of potassium hydroxide in ethanol solution. Treatment of the benzylthio compound with chlorine in aqueous acetic acid, followed by reaction of the resulting sulfonyl chloride with ammonia, afforded 5-chloro-2-nitrobenzenesulfonamide, with a melting point of 159° to 160°C (found: N, 11.71; Cl, 14.53). Reduction of the latter with iron filings and ammonium chloride solution yielded 2-amino-5-chloro-benzenesulfonamide, with a melting point of 152° to 153°C, λ_{max} (MeOH), 253 mμ (ϵ, 12600), 321 mμ (ϵ, 3100); λ_{max} (Nujol), 6.14 μ (found: N, 13.27; Cl, 17.22) which, upon heating with ethyl orthoacetate at 100° to 110°C, furnished 7-chloro-3-methyl-1,2,4-benzothiadiazine-1,1-dioxide (I), with a melting point of 330° to 331°C, λ_{max} (MeOH), 268 mμ (ϵ, 11300), λ_{max} (Nujol), 6.22 μ (found: N, 12.40; Cl, 15.41).

When compound I was administered orally at a dose of 5 mg/kg per day (in two divided doses) to renal hypertensive dogs, a gradual (in 2 to 6 days) fall in blood pressure was observed, which was maintained for the duration of the experiment (12 days) without evidence of diuresis. Upon withdrawal of the drug, the blood pressure returned to approximately pretreatment levels in 3 to 6 days. Essentially similar antihypertensive effects were obtained by using metacorticoid hypertensive rats. These results have also been confirmed clinically, the extent of the pressure reduction in many cases exceeding that observed with the benzothiadiazine diuretics.

Chemically, compound I differs importantly from the diuretic 1,2,4-benzothiadiazine-1,1-dioxides in being devoid of the benzenoid sulfamyl group. Further experiments have indicated that other compounds of this type and other classes of compounds which differ from known diuretic sulfonamides in that the sulfamyl group is replaced by hydrogen, alkyl, halogen, trifluoromethyl, or the like, demonstrate a similar antihypertensive activity separate from diuretic action. It thus appears, from our studies, that removal of the sulfamyl group from substances having diuretic properties usually results in compounds without diuretic effect but exhibiting antihypertensive activity. We are synthesizing and biologically evaluating an extensive series of these compounds.

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5 May 1961

Stereotypy and Intermittent Reinforcement

Abstract. Three pigeons were trained to peck at a horizontally oriented rubber srtip 10 in. long. The spatial distribution of responding along this strip is found to be nonrandom when every peck is reinforced with food. The degree of nonrandomness increases markedly when the pecking is intermittently reinforced.

Antonitis demonstrated that hungry rats will form strong preferences for particular locations when they are given equal opportunities to be fed at a number of different locations (*1*). The experimental situation he used consisted of a box that had a long, narrow, horizontal slot in one wall, and the rat was given a single pellet of food after it put its snout into any part of the slot. Each rat developed a marked preference for some location along the slot. Later, Antonitis discontinued de-

livering pellets for this behavior and found that as the behavior disappeared it went through a phase of much-increased variability. Other experimenters (*2*) have also noted an increase in the variability of a learned response during the course of its extinction, and some have commented on the adaptiveness of this increase in bringing out new forms of behavior.

Antonitis reported that the stereotypy of responding returned when the behavior was again reinforced with pellets. The stereotypy after reconditioning was even greater than the stereotypy during the original training. These findings of Antonitis raise an interesting question about the relation between variability of responding and intermittency of reinforcement. The increase in variability during extinction suggests that a schedule of reinforcement that does not reinforce every occurrence of the selected response will generate more variability than a schedule that does. The heightened stereotypy in reconditioning seems to imply the opposite, namely that a schedule in which the animal is intermittently reinforced (that is, reconditioned) will generate less variability.

The experiment reported here (*3*) was an attempt to establish merely whether variability increases or decreases as a result of intermittent reinforcement. Pigeons were used as subjects in an experimental chamber that contained a 10-in. by 1-in. rubber strip horizontally centered on one wall. A feeding device could be activated to give the pigeon access to grain for about 3 sec. The pigeons were trained to peck at the rubber strip, and the location of the peck was automatically recorded within one of ten 1-in. squares. Three pigeons were used.

In the first phase of the experiment, any peck on the rubber strip operated the feeding device. Approximately 2 wk of daily experimental sessions were conducted; each session consisting of 60 reinforcements. In the second phase, the pigeons were reinforced according to a variable-interval schedule. Pecking the rubber strip operated the feeding device every 3 min, on the average. The range of time intervals between reinforcements in this schedule was from about 5 sec to about 7 min. Reinforcements were still given without respect to the location of the peck on the rubber strip. Sessions were again conducted until the pigeon received 60 reinforcements.

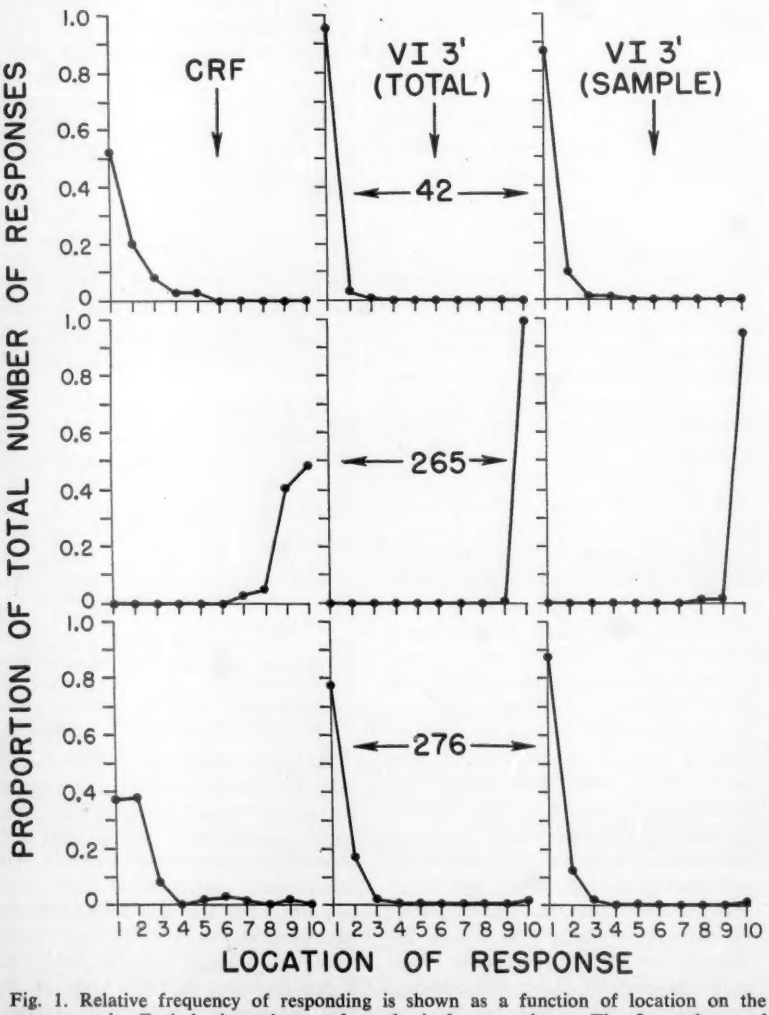

Fig. 1. Relative frequency of responding is shown as a function of location on the response-strip. Each horizontal row of graphs is for one pigeon. The first column of graphs is for a schedule of continuous reinforcement; the second and third columns are for intermittent reinforcement.

Figure 1 summarizes the result of the experiments. Each horizontal row of graphs is for one pigeon; each vertical column for a particular measure of behavior. The points on the graphs are medians from five sessions. In each graph, frequency of responding, expressed as a proportion of the total frequency of responding, is shown as a function of the location on the rubber strip. The ten locations are numbered 1 to 10, going from left to right. The area under each graph approximates 1.0. The first column of graphs, labeled "CRF," (that is, continuous reinforcement) shows the distribution of responding obtained when each peck to the strip was reinforced. A horizontal line at 0.1 would indicate a random distribution of responding, and these graphs make it clear that some degree of stereotypy is present. Each pigeon manifests a tendency to peck at one or the other end of the rubber strip. The second column of graphs shows that the intermittent schedule of reinforcement ("VI 3'" or variable interval of 3 min) produced increased stereotypy. With the first procedure the modal location got between 40 and 52 percent of the responding, with the second procedure the range was from 78 to 99 percent. This increase in stereotypy was evident in the very first experimental session with intermittent reinforcement. The continuous records of location of responding showed that there was increased responding on the modal loca-

tion after about 15 min of the first session and that the final level was reached by the second or third session.

The third column of graphs is a check on possible artifacts in the results. Under the first procedure, the pigeon moved away from the rubber strip after every peck in order to go to the feeding device. Under the second procedure, only a small fraction of the pecks were followed by a movement to the feeding device. It seemed possible that the return to the rubber strip after eating caused a certain amount of variability in the location of responding. This factor would dominate the first procedure, but would be only negligible in the second. The third column of graphs is therefore based on only those pecks, under the variable-interval schedule, that immediately followed eating. Since there were 60 reinforcements in each session, this sample included 59 pecks per session. The distributions of responding in the third column show as much stereotypy as those in the second. It is therefore evident that the increase in stereotypy produced by intermittent reinforcement is due neither to the animal's being forced to move around in the situation nor to the large difference between the numbers of responses that entered into the computation of the first and second columns of graphs.

The duration of sessions under continuous reinforcement was about 10 min; under variable-interval reinforcement it was about 3 hr. This difference in time may have been responsible for the difference in variability under the two procedures. The distributions of responding during the first 10 min of sessions under variable-interval reinforcement make this explanation implausible. The amount of variability seen here was greater than that shown in the second and third columns of Fig. 1, but was still well below the amount shown in the first column.

This experiment strongly suggests that stereotypy is enhanced by intermittency of reinforcement itself and not by some essentially trivial concomitant of the change in procedure from continuous to intermittent reinforcement. Stereotypy is to be expected when there is no benefit to the animal for moving around in the situation. The principle of reinforcement predicts that a location that is reinforced early in the animal's exposure to the procedure would gradually come to dominate the distribution of responding. Moreover, the spread of responding in extinction is empirically, although not theoretically, expected. Why responding becomes more stereotyped during intermittent reinforcement does not, however, follow easily from our present state of knowledge. The clarity of the present findings indicates that a significant but unexplored principle may be involved.

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27 February 1961

A Bacteriophage Specific for F— Salmonella Strains

Abstract. A bacteriophage is described which grows on recipient (F—) and not on donor (Hfr, F+, or F') salmonella. The reason for this differential is unknown, since the phage attaches to all mating types, but progeny ensue only from female bacteria. Purification of this phage has been accomplished. A procedure is described for quantitatively determining either the acquisition or loss of the F agent by bacteria.

Loeb (*1*) and Loeb and Zinder (*2*) reported on a bacteriophage, f2, which would differentiate donor (F+ or Hfr) from recipient (F—) *Escherichia coli* K-12. The phage grows only on donor bacteria. Zinder (*3*) described a staining reaction involving the interaction of *Salmonella typhimurium* strains and *Escherichia coli* strains which could be used to differentiate donor and recipient *S. typhimurium* and *E. coli*. The present report describes a bacteriophage which grow only on recipient *S. typhimurium* strains and not on donor strains. Hereafter, donor strains are referred to as males and recipients as females.

The bacteriophage SP6 was isolated from sewage some years ago by Lederberg (*4*) as one that would grow on *S. typhimurium*, and it was in the collection of salmonella phages listed by Zinder (*5*). In the course of developing some bacterial mutants that were resistant to SP6 for use as a genetic marker in studies (*3*) of recombination in *S. typhimurium* LT2, it was noted that the phage failed to grow on the male bacteria. Since LT2 is female (*3*), as are all but certain of its derivatives, it was possible to compare the growth of SP6 on a whole series of male cultures for which the immediate female ancestor was available. With ten such paired cultures, SP6 grew with equal efficiency on the females but with an efficiency of less than 10^{-6} on males. The male set included eight F+ (*6*, *7*) strains, one F' strain (*8*), and one Hfr strain (*6*). The techniques for isolating such salmonella strains were described by Zinder (*3*). It was noted that when the phage was plated at high concentration on F+ and F' strains (but not when it was plated on Hfr strains) there was some clearing in the background of the plates but in an amount insufficient to form discrete plaques. This is because F' and F+ strains both contain significant numbers of F— "mutants." The technique for demonstrating this will be described later.

To verify further this correlation of phage sensitivity and mating type, the inheritance of sensitivity to SP6 was studied. The criterion used to determine mating type of the progeny of a cross was based on the staining reaction. Two crosses were done with the same pairs of selective markers, except that in one the male was an F+ and in the other an Hfr which had been derived from it. In *Salmonella typhimurium* as in *Escherichia coli*, the progeny of an F+ by an F— cross are generally F+, while progeny from Hfr by F— crosses are F—. The crosses were histidine-requiring males by a leucine-requiring female. Progeny were selected on the basis of nutritional independence. The progeny were isolated, purified, and then tested for the staining reaction and phage sensitivity. There was a perfect correlation in the F status of the progeny as determined by these two criteria. Ninety-five percent of the progeny from the F+ cross were F+, and only 2 percent of the progeny from the Hfr cross had the F agent.

Another test of the correlation of phage sensitivity with mating type could be based on the fact that with *E. coli* there is efficient transfer of F by the simple growth of F+ and F— organisms in mixed culture (*6*, *7*). This does not occur with Hfr cultures. With

most LT2 cultures, however, there is little if any mating in liquid culture and little if any transfer of F (*9*). However, LT2 mates and transfers F well on solid media. After mixed growth of the appropriate cultures on solid media and reisolation of the two input types on the basis of some neutral marker such as galactose fermentation, there was again a perfect correlation of the staining reaction and phage sensitivity. The F+ and the Hfr culture transferred F, as would be predicted from their mating behavior; there was a high efficiency of transfer by the F+ and a low efficiency by the Hfr.

From the foregoing it can be concluded that the bacteriophage SP6 is excluded by the presence of the F agent.

It can be shown that SP6 does not attach differentially to male and female bacteria as does f2 (*2*). When young broth-grown cultures of male and female bacteria are prepared, it is found that SP6 attaches equally well to both strains. Both strains are in fact killed, but the males do not release any progeny, nor do they lyse. The female culture lyses after a latent period of about 15 minutes, and gives a yield of some 20 infective particles per infected bacterium.

Bacteriophage SP6 has been readily purified by ammonium sulfate precipitation (2*M*) followed by alternate cycles of high- and low-speed centrifugation. There are only minor losses in viability during the course of purification. Nucleases were added during the purification; after resuspension, the final high-speed sediment was dialysed against phosphate-saline buffer at *p*H 7.2. These purified phage preparations exhibited the typical absorption spectrum of a bacteriophage solution. The ratio of the optical density at 260 mμ to 280 mμ was 1.5 with an optical density of 5.5 per 10^{12} plaque-forming units. The diphenylamine reaction for deoxypentose as calibrated with calf thymus nucleic acid gave a value of 1.6 μg of deoxyribonucleic acid per 10^{10} plaque-forming units. No significant amount of ribonucleic acid, as measured by the orcinol reaction, could be found. SP6 has an amount of nucleic acid similar to that found in the T-even coliphages (*10*).

Phage-resistant mutants can be selected from the F− strains which retain their properties as females. These fail to attach SP6 at a measurable rate. Since the resistant mutants are not killed by SP6, this resistance can be readily differentiated from the resistance exhibited by male bacteria and, as such, can be used as a genetic marker in bacterial crosses. The gene-determining phage resistance segregates quite independently of mating type.

Bacteriophage SP6 does not attach to either male or female *Escherichia coli* K-12 strains. F− *E. coli* cells which are growing in mixed culture with F+ cells would be rapidly permeated by the F agent and converted to F+. In salmonella strain LT2 it can readily be shown that there is no detectible transfer of F in liquid culture. Therefore, barring selective growth of F+ cells, any losses of F would be maintained in their true proportion in the culture. Since SP6 kills both male and female bacteria, some indirect procedure is necessary to score females in the presence of males. The procedure is as follows. Male populations are treated as desired and then plated on eosin-methylene blue medium without any sugar (*3*) at a density of 2 to 300 colonies per plate, with as many replicate plates as deemed necessary. The plates are incubated until a colony some 2 to 3 mm in diameter has formed. The colonies are then sprayed with a solution of SP6 and further incubated for 4 hours. At this time the plates are screened for mottled and unmottled colonies. The mottled ones are phage sensitive and hence F−. The use of this procedure was verified by setting up mixtures with known numbers of male and female cells. Spontaneous losses of F, which were verified by the staining reaction and by behavior in mating, have been obtained. The average recently purified F+ or F′ salmonella culture has between 1 in 1000 and 1 in 10,000 F− cells.

There are now a variety of techniques, in addition to mating behavior, by which donor and recipient bacteria in the *Salmonella* and *Escherichia coli* group can be differentiated. The one described here sharpens the analogy between the F agent and a prophage. Prophages always impose on their host bacteria immunity to superinfection by the particular phage that they represent. In addition, they may often provoke immunity to unrelated phages. Note here, in particular, the exclusion by lambda-carrying *E. coli* of the coliphage T4 (*11*). Thus "immunity" need not indicate any immediate relationship between the carried and the superinfecting element. It would therefore be premature at this time to infer any such relationship between the F agent and SP6. Further experimentation may shed some light on this point.

NORTON D. ZINDER
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9 March 1961

Partial Metamorphosis in Anomia simplex

Abstract. Many larvae of the common bivalve, *Anomia simplex*, when grown under laboratory conditions, exhibited a partial metamorphosis. They attained a considerably larger size than that at which larvae normally set. The partial metamorphosis was also characterized by the disappearance of velum, but the retention of a functional foot. Moreover, these organisms were not able to attach to the substratum, and their shells showed a distinct demarcation line between larval and adult portions.

The plain jingle shell, *Anomia simplex*, is a common bivalve of our Atlantic coast. In Long Island Sound its period of reproduction occurs virtually simultaneously with that of the American oyster, *Crassostrea virginica*, and during a large part of the summer the larvae of both these species, which to some extent resemble each other, are found in plankton. *Anomia simplex* is one of approximately 20 species of bivalves, the larvae of which have been grown from eggs to metamorphosis at our laboratory (*1*). An interesting observation was made during our studies of *A. simplex* of what appeared to be partial metamorphosis of its larvae and is described in this report.

Metamorphosis, or setting, of *A. simplex* larvae may begin when they are only about 180 to 195 μ long. More commonly, however, this event occurs

when the individuals are approximately 200 μ long, although the largest swimming larvae found in our cultures measured 215 by 210 μ.

Normally, larvae of *A. simplex* approaching metamorphosis drop to the bottom and begin crawling by means of a strong foot, which is developed during the late swimming stages. Upon finding a clear hard area, such as an oyster shell or rock, the metamorphosing organisms attach to it by means of a special byssus that later becomes calcified. From then on a young *Anomia* is unable to move, and it soon completes the process of metamorphosis which, in part, consists of a resorption and disappearance of the foot and velum. Meanwhile, well-developed gills become visible through the semitransparent shell.

In our cultures, however, we observed hundreds of individuals, which were considerably longer than 215 μ, but which were, nevertheless, still crawling on the bottom by means of a ciliated foot. The largest individual, which possessed such a well-developed foot but no velum, measured 577 by 514 μ. All these animals had certain features in common, namely that, although the gills were already well formed and the velum was entirely absent, the powerful functional foot was still present and the animals remained unattached. The last two conditions clearly indicated that the young mollusks had not yet entirely metamorphosed.

Closer examination of these individuals showed that they all had another peculiarity in common—the presence of a definite narrow band in their shells which, apparently, indicated the edge of the prodissoconch, or larval shell, and the beginning of the dissoconch or postlarval shell (Fig. 1). The dividing band was probably formed during an important event in the life of the young mollusks, possibly at the time the velum was resorbed or when some other equally important anatomical or physiological change occurred. Measurement of the inner, prodissoconch, shells surrounded by this band usually gave a

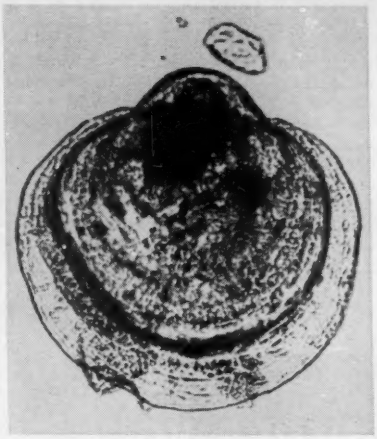

Fig. 1. Photomicrograph of young *Anomia simplex* during the stage of delayed metamorphosis. A definite line dividing prodissoconch and dissoconch portions of the shell and part of the protruding, still functional foot are visible. The size of the organism is about 255 μ.

length of approximately 200 μ, the size at which setting or metamorphosis of the majority of normal larvae occurs. This older portion of the shell, surrounded by the band, was usually somewhat darker than the outer, more recently formed portion.

Fortunately, we also observed several recently attached individuals which, before setting, had passed through the stage of partial and delayed metamorphosis but which, nevertheless, finally succeeded in attaching to the substratum. In all cases a formerly large foot was in the latest stages of resorption, thus indicating that these young mollusks were completing an abnormally prolonged metamorphosis.

Several reasons may be advanced to explain why some individuals could not normally metamorphose at the proper time. One possibility is that either the absence or presence of some substance in the water, in which the larvae were grown, interfered with the normal progress of metamorphosis. The second, and perhaps more probable explanation, is that the normal setting of larvae was delayed because they could not find the proper substratum for attachment. The importance of such environmental factors, often affecting settling and metamorphosis of many invertebrates in aquatic communities, was well reviewed by Wilson (*2*).

In some of Wilson's early experiments it was clear that the condition which caused the delay in metamorphosis of larvae was the lack of sand on the bottom. Wilson suggests that phenomena of this kind may be general, and the choice of the substratum on which the metamorphosing organisms wish to settle depends as much on its microbiological characteristics as upon its chemical and physical characters. Since, in our experiments, all the vessels in which the cultures of *A. simplex* were grown were of glass, perhaps the smoothness of the material and its composition did not offer the necessary chemical or physical stimulus for normal metamorphosis. However, although the explanations are plausible, they do not appear to be well based because they fail to explain why only certain individuals in the cultures behaved in an abnormal way, while others, usually the majority, metamorphosed normally at the expected size. Nevertheless, our observations of partial metamorphosis of *A. simplex* suggest many interesting experiments on this and related species that may help us to understand and explain certain aspects of the importance of various chemical and physical factors in the environment, especially of the substratum, on metamorphosis of lamellibranch larvae.

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8 March 1961

Meetings

Forthcoming Events

July

24–29. Medical Electro-Radiological Societies, Latin Federation of, 5th congr., Paris, France. (C. Proux, Secretary, 9 rue Daru, Paris 8)

24–30. Urology, 12th intern. congr., Rio de Janeiro, Brazil. (J. Silva de Assis, Secretary, P.O. Box 1275, Belo-Horizonte, Brazil)

26. International Commission for the Prevention of Alcoholism, 7th annual meeting, Washington, D.C. (International Headquarters, 6840 Eastern Ave., NW, Washington 12)

26–28. Detection and Assay of Hormones by Immuno-Clinical Means, Ciba Foundation Colloquium (by invitation only), London, England. (Ciba Foundation, 41 Portland Pl., London, W.1)

27–1. Macromolecular Chemistry, intern. symp., Montreal, Canada. (Organizing Committee, P.O. Box 816, Sarnia, Ontario, Canada)

28–29. Linguistic Soc. of America, Austin, Tex. (A. A. Hill, Box 7790, University Station, Austin 12)

30–2. Soil Conservation Soc. of America, Lafayette, Ind. (H. W. Pritchard, 838 Fifth Ave., Des Moines 14, Iowa)

30–3. International Psycholanalytical Congr., 22nd, Edinburgh, Scotland. (Miss C. de Monehaux, 53 York Terrace, Regents Park, London, N.W.1, England)

31–4. American Crystallographic Assoc., Boulder, Colo. (W. M. Macintyre, Univ. of Colorado, Boulder)

31–4. Biophysics, 1st intern. congr., Stockholm, Sweden. (B. Lindström, Dept. of Medical Physics, Karolinska Institutet, Stockholm 60)

31–4. Differential Equations in Non-Linear Mechanics, Air Force Acad., Colorado Springs, Colo. (J. P. Lasalle, 7212 Bellona Ave., Baltimore 12, Md.)

31–11. Physics of the Solar System and Re-entry Dynamics, conf., Blacksburg, Va. (Bureau of Public Relations, Virginia Polytechnic Inst., Blacksburg)

31–12. Electric Power and Problems of Nuclear Power, seminar, U.N. Economic Commission for Latin America, Mexico, D.F. (A. Dorfman, Chief, Energy and Water Resource Program, Avenue Providencia 871, Santiago, Chile)

August

1–26. Functional Analysis, 8th American Mathematical Soc. summer institute, Stanford, Calif. (P. D. Lax, AMS, 190 Hope St., Providence 6, R.I.)

2–5. International Conf. of Pure and Applied Chemistry, 21st, Montreal, Canada. (R. Morf, Hoffmann-LaRoche, S.A., Grenzachterstrasse 124, Basel, Switzerland)

3–5. Canadian Chemical Conf. and Exhibition, 44th, Montreal. (Chemical Inst. of Canada, 48 Rideau St., Ottawa 2, Ont.)

4–1. Pennsylvania Acad. of Science, 36th summer, Grove City. (J. J. McDermott, Franklin and Marshall College, Lancaster, Pa.)

5–9. International Rorschach Soc., 14th congr., Fribourg-en-Brisgau, Germany. (A. Friedemann, Chemin des Pêcheurs 6, Bienne, Switzerland)

6–10. Occupational Medicine and Toxicology, 3rd Inter-American conf., Miami, Fla. (W. B. Deichmann, School of Medicine, Univ. of Miami, Coral Gables, Fla.)

6–12. Atmospheric Ozone and General Circulation, symp., Arosa, Switzerland. (H. U. Duetsch, 20 Carl Spittelerstrasse, Zürich 53, Switzerland)

6–12. Chemical and Thermodynamic Properties at High Temperatures, symp., Montreal, Canada. (N. F. H. Bright, Natl. Research Council, Ottawa, Canada)

6–12. International Congr. of Pure and Applied Chemistry, 18th, Montreal, Canada. (L. Marion, Natl. Research Council, Ottawa 2, Canada)

7–9. Guidance and Navigation Conf., American Rocket Soc., Palo Alto, Calif. (J. J. Herford, ARS, 500 5th Ave., New York, N.Y.)

7–9. International Committee of Electro-Chemical Thermodynamics and Kinetics, 13th meeting, Montreal, Canada. (N. Ibl, Eidg. Technische Hochschule, Laboratorium für Physikalische und Elektrochemie, Universitätsstrasse 6, Zürich 6, Switzerland)

7–9. Space Age Astronomy, intern. symp., Pasadena, Calif. (D. W. Douglas, Jr., Douglas Aircraft Co., Inc., Santa Monica, Calif.)

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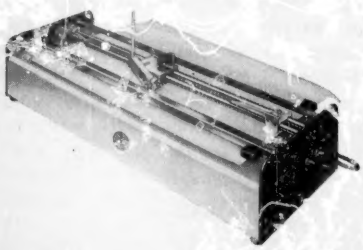

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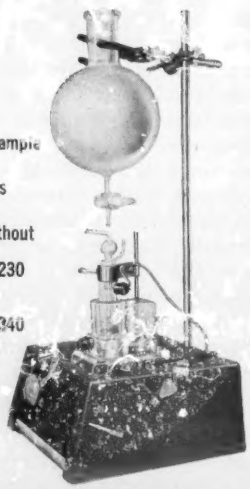

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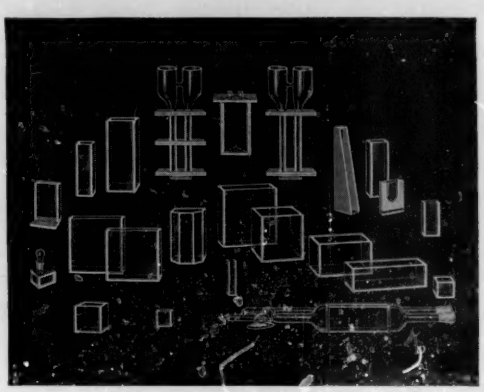

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7–11. High Temperature Chemistry and Thermodynamics, symp., Montreal, Canada. (L. Brewer, Dept. of Chemistry, Univ. of California, Berkeley)

7–11. Seminar on Fast and Intermediate Reactors, International Atomic Energy Agency, Vienna, Austria. (IAEA, 11 Kärtner Ring, Vienna 1)

8–11. Poultry Science Assoc., State College, Pa. (C. B. Ryan, Texas A & M College, College Station)

8–16. Society of Protozoologists, Prague, Czechoslovakia. (N. D. Levine, College of Veterinary Medicine, Univ. of Illinois, Urbana)

10–16. International Congr. of Biochemistry, 5th, Moscow, U.S.S.R. (N. M. Sissakian, Leninsky prospekt, 33, Moscow, B-71)

10–16. International Union of Biochemistry, 4th general assembly, Moscow, U.S.S.R. (R. H. S. Thompson, IUB, Dept. of Chemical Pathology, Guy's Hospital Medical School, London, S.E.1, England)

12–19. Fast Reactions, summer school, Cambridge, England. (Secretary of the Summer School, Dept. of Physical Chemistry, Lensfield Road, Cambridge)

13–18. Microchemical Techniques, intern. symp., University Park, Pa. (H. J. Francis, Jr., Pennsalt Chemical Corp., P.O. Box 4388, Chestnut Hill Post Office, Philadelphia 18, Pa.)

13–18. Theoretical Aspects of Magnetohydrodynamics, seminar, University Park, Pa. (Conference Center, Pennsylvania State Univ., University Park)

13–19. International Assoc. of Applied Psychology, 14th congr., Copenhagen, Denmark. (Congress Secretariat, 19 Sankt Pederstraede, Copenhagen K.)

13–19. Training for Research in the Processes of Vision, 1st intern. conf., Rochester, N.Y. (Office of Public Information, River Campus Station, Rochester)

14–17. Calorimetry Conf., intern., Ottawa, Canada. (J. E. Kunzler, Bell Telephone Laboratories, Murray Hill, N.J.)

14–19. International Medical Conf. on Mental Retardation, 2nd, Vienna, Austria. (Miss E. Langer, Div. of Maternal and Child Health, State House, Augusta, Maine)

14–19. Symposium on Radiation, Vienna, Austria. (World Meteorological Organization, 1 Avenue de la Paix, Geneva, Switzerland)

14–25. Israel Medical Assoc., 5th world assembly, Jerusalem, Israel. (Beth-Harofeh, 1 Heffman St., Tel-Aviv, Israel)

14–26. Plant Pathology, conf., Lafayette, Ind. (J. F. Schafer, Dept. of Botany and Plant Pathology, Purdue Univ., Lafayette)

14–26. World Eucalyptus Conf., 2nd, São Paulo, Brazil. (Intern. Agency Liaison Branch, Office of the Director General, Food and Agriculture Organization, Viale delle Terme di Caracalla, Rome, Italy)

15–17. International Assoc. of Milk and Food Sanitarians, Jekyll Island, Ga. (H. L. Thomasson, P.O. Box 437, Shelbyville, Ind.)

15–18. Technical Assoc. of the Pulp and Paper Industry, 12th testing conf., Montreal, Canada. (TAPPI, 155 E. 44 St., New York 16)

15–24. International Astronomical Union, 11th general assembly, Berkeley, Calif. (D. H. Sadler, Royal Greenwich Observatory, Hailsham, Sussex, England)

16–18. Hypersonics Conf., intern., Cambridge, Mass. (J. J. Harford, American Rocket Soc., 500 Fifth Ave., New York, N.Y.)

18–21. Association of American Geographers, East Lansing, Mich. (M. F. Burrill, 1785 Massachusetts Ave., NW, Washington 6)

19–30. Agricultural Economists, 11th intern. conf., Cuernavaca, Mexico. (J. Ackerman, Farm Foundation, 600 S. Michigan Ave., Chicago, Ill.)

20–23. International Ergonomics Assoc., 1st congr., Stockholm, Sweden. (T. Olson, Dept. of Industrial Physiology, G.C.I. Lidingövägen 1, Stockholm)

20–24. American Veterinary Medical Assoc., Detroit, Mich. (H. E. Kingman, AVMA, 600 S. Michigan Ave., Chicago 5, Ill.)

21–23. International Hypersonics Conf., Cambridge, Mass. (F. Ridell, Avco Research Laboratory, 301 Lowell St., Wilmington, Mass.)

21–24. Biological Photographic Assoc., Chicago, Ill. (Mrs. J. W. Crouch, Box 1668, Grand Central P.O., New York 17)

21–24. International Conf. on Photoconductivity, Ithaca, N.Y. (E. Burstein, Dept. of Physics, Univ. of Pennsylvania, Philadelphia)

21–26. International Congr. of Psychotherapy, 5th, Vienna, Austria. (W. Spiel, Lazarettg. 14, Vienna 9)

21–26. World Traffic Engineering Conf., Washington, D.C. (Intern. Road Federation, 1023 Washington Bldg., Washington 5)

21–27. International Assoc. of Dental Students, congr., London, England. (D. H. Clark, Royal Dental Hospital, Leicester Sq., London, W.C.2)

21–31. United Nations Conf. on New Sources of Energy, Rome, Italy. (United Nations, New York, N.Y.)

21–2. International Congr. of Practical Medicine, Merano, Italy. (Bundesärztekammer, 1 Hädenkampfstrasse, Cologne, Germany)

21–6. Pacific Science Congr., 10th, Honolulu, Hawaii. (Secretary General, 10th Pacific Science Congr., Bishop Museum, Honolulu)

22–25. International Pharmacological Meeting, 1st, Stockholm, Sweden. (A. Wretlind, Karolinska Institutet, Stockholm 60)

22–30. International Conf. on Protozoology, Prague, Czechoslovakia. (N. D. Levine, College of Veterinary Medicine, Univ. of Illinois, Urbana)

23–25. Gas Dynamics, symp., biennial, Evanston, Ill. (J. J. Harford, American Rocket Soc., 500 Fifth Ave., New York, N.Y.)

23–26. Electron Microscope Soc. of America, Pittsburgh, Pa. (Miss M. L. Rollins, Agricultural Research Service, U.S. Department of Agriculture, P.O. Box 19,687, New Orleans 19, La.)

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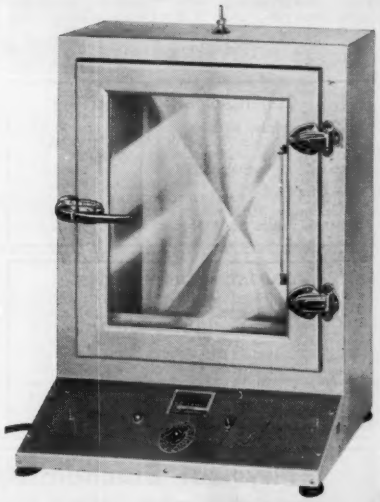

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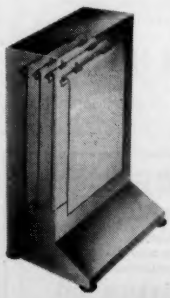

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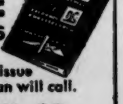

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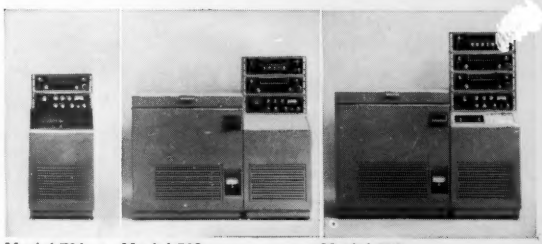

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